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ANNALS OF INTERNAL MEDICINE

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DEPARTMENT OF REVIEWS

The Journal will make an especial feature of the review of monographs and books bearing upon the field of Internal Medicine. Authors and publishers wishing to subject such material for the purposes of review should send it to the editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all matter sent will be made in the department of reviews.

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Presidential Address*

(American College of Physicians)

By Frank Smithies, M.D., Sc.D., *Chicago*

In the past, the parting words of your retiring president have dealt largely with the national and international necessity for such an organization as The American College of Physicians. This vindication of our society does not require reiteration; very little if anything, can be said supplementary to the masterly addresses delivered by former Presidents James M. Anders, Harlow Brooks and Alfred Stengel. In no uncertain way, have these gentlemen defined the fields of endeavor open to The College and most potently have they emphasized for us and the curious, if not critical, the pressing urge for just such grouping of internists and research workers as now comprise our membership. Furthermore, former Presidents have practiced what they preached: no one, not intimately connected with The College adequately can appraise what of influence, time and physical energy these men unselfishly have given to advance the growth, the rating, academic and ethical, and the financial stability of our organization. Without their help your College could not have developed to its present significance: nay, it is doubtful whether it could have continued to exist. Our gratitude should be everlasting: most certainly, as time passes, the work of those pioneers will assume larger meaning when decades permit the proper perspective.

On the present occasion, it would appear not altogether useless that your speaker bring to your attention certain achievements of The College, place before you its structure and status and inform you of what is to be ventured.

In the lives of all organizations, as in the lives of individuals, it is wisdom, at intervals, to take stock, to appraise, to calculate liabilities and assets, to recognize strength but not at the expense of disregarding weakness. Only by the rigid and impartial scrutiny is advance along suitable lines intelligently to be made. In your speaker's opinion, at this session one should dwell not on justification for the existence of The American College of Physicians—such meetings as the present answer what doubt there may have been in that regard—but should survey the paths which have been trodden in order that progress along the highway before us shall continue to be travelled with dignity, respectability and usefulness.

*Delivered before the American College of Physicians, March, 1928, New Orleans, La.

In May of this year, the American College of Physicians will have been in existence twelve years. While in some quarters, in 1915 doubt was held regarding whether or not the College were properly launched, yet, it *was* launched. No one, honestly, can question the high motives, ideals or enthusiasm with which the sponsors of The College took up their tasks.

As a direct answer to those who criticise the early career of the College,—and it may be said the harshest criticism came from those who were least familiar with the venture—it is interesting to know that in the first five years of its existence (up to 1920) but 230 physicians and laboratory workers had been admitted to Fellowship. This group was comprised largely of physicians in New York and nearby cities. Study of the personnel at this period demonstrates that it represented practitioners of internal medicine above the average in the section embraced. The fellowship roll included a goodly number of internists of national prominence. Careful search of the roster of the early members fails to disclose a single scoundrel or irregular practitioner. I mention this, because, during its early days, the College faced such accusations and some even stronger, the echo of which injustice may be recognized even today if one have his ear close to the ground.

Beginning with 1921, at the Baltimore annual clinical week, The College became for the first time, an organization destined to include all qualified, progressive practitioners of internal medicine throughout the American continent. Such increased scope was possible only because a wholly unselfish, disinterested group of men, who were then called Councillors, saw what advantages to internists would arise from an organization supporting the cause of the internist in the field of medicine and from the opportunity for their association in a continent-wide group. These councillors gave liberally of their experience, time and funds, so that a suitable organization for creating representative and more highly skilled internists might become possible. These councillors were fortunate in securing the advice and guidance of many of the most representative teachers and clinicians of the country. Nothing was done hastily. Indeed, it was not until 1924, nearly ten years after the College had been incorporated, that those who were interested in the movement, felt that foundations of such strength had been laid as to warrant permanency and service. There was no hurried drive for members. There was close scrutiny of applications for fellowship. Election to fellowship by the then regents represented the opinions of an eminent board regarding the desirability of a candidate. Indeed, the American College of Physicians never has carried on a "drive" for membership such as has been commonly conducted by our greatest national organizations. Many applications for fellowship came to the Secretary-General's office spontaneously or, from physicians who already had attained fellowship and were desirous that their associates do likewise. This situation exists today. Without "barn-storming" or regional or sectional campaigns, the

enrollment of the fellows has risen from 230 in 1915 to 1507 in 1928. In addition to this great fellowship roster, there are now 600 associates.

The Fellows of the College do not constitute a non-representative, incapable and unimportant group. This is demonstrated emphatically by perusal of the 1927-28 Year Book. The roster shows that approximately 40% of the total number of Fellows are engaged in a teaching capacity, either as part or full-time men. Further, by this group every first grade school of medicine in the United States and Canada is represented. In the case of numerous institutions, practically the entire clinical and research faculties, including and above the grade of instructor, are Fellows of the College. In fact, there are but four A grade institutions in the teaching of medicine in the United States and Canada whose leading clinicians are not at present enrolled on the College roster. In addition to the 40% of Fellows who are actively engaged in medical teaching, practically the entire medical and laboratory personnel of our public services (Army, Navy and Public Health), from those occupying the highest posts to those in positions corresponding to instructorship in reputable colleges, are active and enthusiastic members. The College likewise honors the only medical man in President Coolidge's cabinet. Finally, more than 90% of those Fellows who are so situated geographically as not to be in close relationship to teaching institutions are heads or important members of their staffs in first rank hospitals or clinics. In the majority of instances, these men have a most important influence in directing and maintaining scientific and ethical standards in the institutions and communities in which they practice. Many of these men conduct important medical clinics for the instruction of brother practitioners. They are teachers in nurses' training schools, directors of municipal and state health laboratories and carry on a type of medical practice which compares favorably to that observed in any of our leading teaching institutions.

Especially has the College been wise in arranging for a group called "Associates." As at present constituted, the personnel of this group includes a goodly number of men who are connected with teaching institutions and clinics and who are enrolled as "Associates" during what might be termed a "term of probation" or "ripening". In this period, younger men can be kept in close contact with teaching, hospital, laboratory and research work, and, under the guidance of seniors of their services in their communities, approach the time when by high standards of work, ethical practice and scientific contributions, they become eligible to full fellowship in the College. This associate group is becoming and it is proper that it should become, a potent influence for encouraging, supporting and assisting the young physician desirous of making internal medicine his life's work after he has become separated from the stimulus of college, hospital and institutional environment. I look upon this "associate" group as one of the most significant agents for forwarding the best that

exists in American medicine. Previously, many internists of most excellent promise were lost to the practice of internal medicine and as contributors to our literature, because after severing the ties of university and hospital, there was not available to them an organization through which they could receive assistance and to which they could contribute by work or by attendance. It is from such men, frequently located far from so-called medical centers, that medical discoveries of the greatest worth have and may come. Our medical annals are filled with instances, where, as a result of encouragement and timely aid from more experienced seniors, new forms of disease and new types of therapy have become known. For example, a Nevada mining-camp physician demonstrates an early, if not the earliest case of pulmonary sporotrichosis; a Nebraska internist describes the new clinical entity, congenital family oedema; a northern Michigan doctor doing his best to become an internist in spite of the surgical urge of his surroundings, records the spontaneous occurrence of scarlet fever and measles and, another, far from inspiring medical contacts, contributes observations of first rank upon goitre; from a laboratory in a Michigan town of less than 30,000 comes what is now the standard precipitin test for syphilis; two Arizona physicians record and describe endemic Malta fever; a young Mississippi doctor, upon encouragement and opportunity, performs the most important piece of work upon the transmission and control of malaria since Lavaran's original thesis; our knowledge of sprue and its anemia is advanced from a small North Carolina town; a Missouri physician assembles the greatest pollen collection on the continent; a previously obscure Canadian gives to the world insulin. Time alone prevents the recital of other contributions equally valuable.

The point at issue is how much progress has been lost during the past thirty years because capable men were, by environment, kept from contact with medical men of their kind and deteriorated from lack of encouragement and stimulus? Certainly, one cannot fail to grasp the importance to an "associate" of a group of fellows in his own community or state with whom he can communicate and from whom he can receive suggestions regarding the practical carrying on of work in which he is particularly interested or has an especial bent. Until the organization of The American College of Physicians in its present form, he could not receive this type of stimulus through any organization now existing on the American continent. Is it not reasonable to expect that when our roster includes a thousand "associates" who are eagerly pursuing clinical and research work in an effort to qualify for full fellowship, better practice of medicine will follow in many communities, better hospital organization will result, and from more intensive and intelligent effort, valuable contributions to our knowledge will be made?

From the foregoing, it is evident that the personnel of The Amerian College of Physicians discounts criticism. The group represents a large section of what is best in the acad-

emic, scientific, administrative and practical field of internal medicine on the American continent. It constitutes the only great organization of internists on this continent. It is the only altruistic endeavor to recruit, stimulate and train an oncoming body of young men to keep filled the ranks of ethical, scientific medicine as their seniors choose to lighten their burdens or cease their labors.

That the ethical ideals of the organizers of the College as it at present exists well have been maintained by the Fellows after their election, is strikingly demonstrated by the fact that the Ethical Relations Committee has had to consider less than one-half dozen instances of suspected violations of the Constitution or of our oath from the date of the foundation of the society.

That the College is proving a stimulus to the young internist, is evidenced by its records: within the past year the number of applications for Fellowship and Associateship has been twice as large as in any year in the history of the organization.

One of our greatest accomplishments has been the establishment of an annual clinical week in medicine in one of the great cities of North America. In no other organization on the Continent is it possible for clinicians and laboratory workers to meet annually for a frank discussion of what is actually or is potentially of value in the field of medicine. It is true, that from time to time, national associations have attempted to hold in connection with their annual assemblies, certain clinical conferences, but also, it is true that the attempts of none of these national organizations has been in any way successful. One has but to attend the clinics held on some of these "pre-convention days" to satisfy himself of this observation. The American College of Physicians is the only organization on the American continent which annually meets with the distinctive and definite object of profiting by a week of amphitheatre and bedside medicine or, the observation of laboratory methods in close relation to their elucidation of problems of disease.

That a clinical week in medicine was needed and that it could be made of incalculable value to the internists and teachers, is demonstrated by the increasingly great success of each annual session of the College. To be sure, there exist other organizations which meet and devote time to clinical medicine, but none of these organizations is national. Here and there throughout the land small groups of medical friends or men, who are interested in similar problems, occasionally gather as "interurban" or "clinical" clubs. These meetings are designed so that even men who every day are in contact with a large hospital material as clinicians or as teachers, find it helpful and broadening to discuss patients from the clinical standpoint, to see a man work in his own environment and to observe the social, administrative and scientific problems connected with different institutions. Valuable as these interurban clubs are, unfortunately they are limited in their attendance, largely to the very men who least need clinical or scientific prodding or guidance. Most of the attendants at these sessions already are consid-

ered by others or by themselves to be specialists in their various fields: hence, often the meetings ignore the clinical aspects of medicine and degenerate into wordy debates on abstract topics. However, the existence of these small, local groups or clubs indicates the desirability for clinical and scientific men periodically coming together for readjustment of viewpoints and ideas. If such local (gatherings are of benefit to a few, then no one can gainsay that an annual national or even international conference of internists for similar purposes is not a forward step educationally. If the American College of Physicians had done nothing else but institute and maintain its annual week in clinical medicine, it would have justified its existence.

Certainly, during the past ten years, any internist who has attended the clinical sessions of the College as held at various medical centers throughout America refuses to be satisfied with what previously he has been able to glean from the occasional meetings of local, interurban clubs and their necessarily limited scope. Is it not an unusual opportunity when an internist once a year may secure new outlooks and readjustments of his ideas by mingling with hundreds of representative medical men from all parts of America, from observing institutions and their equipment and from having demonstrated to him types of patients with which he may have been familiar only vaguely through rare contact or but from the literature? Moreover, as the program of this meeting has amply proved, is it not of inconceivable practical worth to internists and to research workers to have presented to them disease symposia, the speakers at which are authorities in their special fields? Upon the programs of none of our national organizations with limited membership or in sections devoted to medicine in our numerically greatest associations is it possible to have assigned five half days and four evenings to an exhaustive discussion of live medical or research problems. From their very nature, other national medical societies, whether they be of research type or be great gatherings of general practitioners, cannot devote time for the thorough discussion of the various phases of internal medicine as is possible at the sessions of this College. For the clinician or laboratory worker who has a sound contribution to make, the clinical week of the College affords an unrivalled opportunity. The constant apprehension of your Regents is that ultimately attendance at these sessions will be so large that only a few cities will be capable of staging the meetings along the comprehensive lines defined by the Fellows and Regents.

Early in the organization of the College, it became apparent to your officers and regents that there was a place in the field of internal medicine for a publication devoted to the linking of clinical observation with laboratory observation and research. To the answer that the medical journalism already had covered all topics, I may say that, with possibly one exception, there exists in this country no periodical exclusively devoted to furthering the interests of internists and affiliated laboratory workers. In medical journals, the art of medicine

as exemplified by Osler, rapidly has been thrust into the background by the weird admixture of various non-related topics in their pages or by the publication of half complete, often purposeless, clinical or research investigations. Granted that all of these magazines are of value, yet, there is no question, that there is demand for a periodical which is concerned solely with the problems of the internist.

The establishment of a new medical journal is not an easy task, particularly when such journal is conducted upon ethical lines with respect to its advertising pages. Great journals are the end products of painful evolutionary effort: they cannot be built and enlarged like sectional book cases. They require healthy original concepts, skillful guidance, maturity by time, and opportunty to create affection and longing in the hearts of those they greet. Your regents have fully been alive to the situation. In their wisdom they prevailed upon Professor Warthin to assume the editorship of your official periodical, the Annals of Internal Medicine. Busily occupied with teaching and investigation as is Professor Warthin, yet, he entered upon his task with enthusiasm. To it he has brought unusual scholastic, scientific and executive ability. Month by month, the College has had presented to it one of the most attractive, medically and culturally valuable, and linguistically correct journals in the world. Young as the publication, is, one has only to pursue current medical literature to observe how frequently reference appears to articles originally published in the Annals. The excellence of Professor Warthin's editorials is marked: not rarely they are quoted *in toto* by leading national periodicals. Book reviews and abstracts are of an unusual kind and completeness.

The circulation of the Annals steadily has increased. At present, even with but approximately 1500 Fellows in the College, the monthly distribution of the periodical is more than 2000 copies. With constant accessions to our membership roll and with the continued high quality and the future enlargement of the Annals, it is safe to say that within as short a period as two years, the journal even without advertising revenue, will not only have one of the largest monthly circulations on this continent, but will be self-supporting. Your speaker regards it as an achievement of the first order that the College has succeeded in so quietly and successfully launching this new publication. Further, the College owns the Annals outright and it will be the policy of the Regents to carefully guard our proprietorship.

Inasmuch as this great body of Fellows meets but annually, a few words with respect to the administrative and financial side of your organization are in order. For about two years, the College has had a thoroughly equipped and up to date central office at Philadelphia. It has been established in close proximity to the University of Pennsylvania and thus absorbs a certain degree of academic tradition and vision. At this office, equipment both with respect to personnel and mechanical appliance, is beyond criticism. Such office manages efficiently the multitudinous details concerned with applications, investi-

gations of the qualifications, academic, professional, ethical and social, of candidates for fellowship, the meetings of various executive officers and committees, correspondence relating to our publications, state and national activities, etc. With an adequate force of assistants, generously provided by the Board of Regents, the Executive-Secretary, in co-operation with the Secretary-General, conducts the affairs of our organization in an intelligent, dignified and prompt fashion. In addition to the routine details, the office arranges the annual sessions and economically transacts the financial business of the organization. It is doubtful if any organization of internists in this country has the affairs of its members so well tabulated and conducted as does the American College of Physicians. The scope of this central office is increasing. Inquiries come to it regarding post-graduate study, the meetings of scientific groups, the standardization and interpretation of laboratory tests, abstracts of literature, problems arising in hospital administration, data concerning the experience and standing of practitioners, hospital equipment, co-operative activities along various professional, social, philanthropic and ethical lines, etc. Thus, it becomes quite evident that as the College develops, its central office will require expansion if it is adequately to assume the increasingly vigorous activities of internists throughout the continent.

It will not be long before the College will require not only an increase in its office staff but even a building for the reception of its members, the housing of its records, the maintenance of a library or a museum. Those who are intimately connected with the affairs of the organization forecast that these requirements can not long be postponed. The College will not go backward; it cannot stand still; it must go forward. In going forward, its activities will broaden far beyond our present conceptions. In view of these circumstances, the question of a permanent home for the American College of Physicians requires immediate consideration. Definite plans toward such should be made. While it may be years before the home of the American College of Physicians will rival that of its sister organization across the water, or of local institutions, as the College of Physicians of Philadelphia, yet, the increase of its affairs will compel expansion. It behooves the Fellows and the executive officers to plan broadly so that at the time of accomplishment, the College will be in possession of quarters commensurate with the dignity, responsibilities and achievements expected of the organization.

The office of the Executive Secretary, together with the assigned Committees and the Regents, have achieved a noteworthy success during the past year in the issuance of a Year Book and a Bulletin of the College. Especially needed was a Year Book listing the Fellows and giving information about them. I know that, in many quarters, perusal of this Year Book has occasioned surprised comment: the surprise being due partly to the excellence of the arrangement of the Year Book but more especially

to the revelations which the Year Book contains regarding personnel.

During the past five years, the College has worked in such a quiet way that many of those who, from ignorance, prejudice or habit have criticised the College were not aware until the Year Book appeared, of the great strides in membership which have been made. The Year Book potently has demonstrated to the internists of North America the wide geographic range of College membership, the high character of its personnel and, incidentally, the interest which internists have taken in an organization devoted exclusively to forwarding their own betterment. This Year Book has become a volume largely in demand in colleges and libraries, newspaper offices and among the medical profession. The volume has proved of great practical worth to physicians in a country where travel over long distance is so common. Patients no longer need be told merely to "see a doctor" in a far distant city but through the Year Book they can be given a definite list of competent internists in the leading cities of our various states and provinces; their physicians can now be assured that his patients will receive skilled care and gentlemanly attention. If physicians heretofore have felt it worth money to subscribe to Year Books, listings of "experts," etc., issued by commercial organizations, surely it is a great accomplishment for the College to have made available to them a Year Book published on a non-commercial basis, a book not merely listing men as "experts" but what is more valuable, namely, data from which it is possible to appraise the professional and social qualifications of far distant practitioners.

The financial status of the College has been but rarely brought before you. It would seem desirable that you have knowledge what your College has accomplished in this regard. Perhaps, you will be interested to know that up to six years ago, the financial status of the College was extremely precarious. There had been no attempt made to acquire funds even for current expenses and certainly none to accumulate a surplus. Much of the expense concerned with the annual meetings, the administrative offices, travel and the like were borne by interested officers or councilors. It was seen, however, that no organization could exist long on such a footing. Through a wise policy instituted about five years ago, and most ably carried out by your Treasurer, the College steadily has accumulated, without donations, contributions or a noisy campaign for funds, a most creditable surplus. Its present assets exceed $65,000. It is able to finance its enterprises and to pay its bills promptly enough to get discounts. Certain of these funds are segregated as an Endowment Fund. The affairs of the College are conducted on a strictly budget basis and every effort is made to carry on most economically. Thus, the money contributed by Fellows is not wasted. Every candidate upon payment of his initiation fee, can feel assured that what he has paid is not lost but is held in trust for his benefit and to foster all that is best in the advancement of internal medicine.

The Constitution and By-Laws specifically provide for the creating of the endowment fund. The purposes of such funds would seem to be not only provision for a permanent home for the College and for maintenance but to make available a sum which the College can employ for encouraging research and for education. It is only within the past year that the Regents have had opportunity seriously to consider putting forth efforts to create an endowment fund of substantial proportions. Already you are familiar with the opportunity which has been given to the Fellows of the College to subscribe, either in lump sum or by installments for life memberships. The sums derived from these life memberships can, almost in their entirety, be placed in the endowment fund. If but one thousand of our Fellows systematically set about the purchasing of life memberships, within three years the Endowment Fund will be sufficiently large as to enable the Board of Regents to provide handsomely toward the carrying out of the purposes for which this fund is intended.

Apart from the academic and clinical attributes of the personnel of the College, it seems highly important that every Fellow appreciate the significance toward extending the influence of the College which a strong financial rating will insure. Much of the success which has attended the efforts of our sister organizations can be attributed to these organizations having available the means whereby they could effectually attack the problems requiring attention and solution. There should be no urging of Fellows to contribute to the Endowment Fund: its creation should not entail great hardships upon anyone. However, it is well known that many of the Fellows are amply able from savings of current earnings to purchase life memberships. These men should feel that it is a privilege thus to contribute something toward the permanency and the expansion of the organization to which for years a small group of Fellow members have given liberally of time, physical effort and money. To a letter recently sent to each Fellow, there has been a noticeable stimulation of interest in the Endowment Fund and a creditable number of Fellows have either paid for life memberships in full or have arranged to take care of payments at intervals. To these men the organization owes deep gratitude. It is expected that in the coming months an increasingly great number of Fellows will do their bit. It is realized that there is a group in the College who on account of the nature of their occupations as teachers, health officers and the like will not be in position to make substantial contributions to the Endowment Fund. A suggestion is made that in these circumstances, men so placed keep the Endowment Fund of the College in mind on occasions when public spirited laymen of their acquaintance express desire to do something in a substantial and material way for the advancement of medical practice and science. In all probability, in every community there are men willing, and ably so, to assist, provided they know along what lines assistance may properly be given. It is the duty of Fellows to ac-

quaint substantial laymen with the opportunities for giving offered by the College and it might be well within the bounds of propriety, when plans have matured, to solicit subscriptions from laymen toward the purchase of a suitable college building. It would be only gratitude on the part of the College that the names of such contributors be perpetuated in enduring fashion by appropriate tablets on the walls of our permanent home.

Time does not permit more than a brief resumé of what the special committees of the College have accomplished during the past two years. I have already acknowledged the debt which the College owes to the Committee on Publications and Year Book for the thorough fashion in which they have worked in order to present to us Annals of Internal Medicine and the College Year Book These men have been greatly helped in their tasks by the support of a loyal and enthusiastic Board of Governors, in fact, in some states, the governors have themselves been largely responsible for the accuracy of data, favorable sentiment toward the College and a steady flow of fellowship applications toward the Executive Secretary's office.

A committee which has been most active and helpful is that concerned with hospital efficiency. Under the guidance of the Board of Regents, this committee has considered exhaustively how the College could be of help to its Fellows in exercising some form of control over the medical, as distinct from surgical, routine and practice in our hospitals. It has been thought wise not to rush hastily into any such program, nor to present to you, to other interested organizations and to hospitals, a program which would be incomplete, a reduplication of effort or an annoyance to the institutions. As you well know, the so-called standardization plan of the American College of Surgeons — the "minimum requirements" program — has meant much toward increasing morale, efficiency and equipment in many of our hospitals, particularly hospitals not located in the larger cities. The data accumulated by the American College of Surgeons has been collected at great expense and effort. The co-operation of hospital authorities has also entailed work and sacrifice on their part. The American Hospital Association likewise has collected much data and has been an influence for good throughout the country. The American Medical Association has made a complete survey of the country's hospitals from the standpoint especially of their furnishing suitable institutions for the training of internes, nurses and with regard to their fitness as places for graduate instruction. One can readily see, therefore, that any activity of the American College of Physicians must be cautiously and intelligently directed. If it is not, then institutions will be annoyed by what they regard as a re-canvass of the field already well covered and in such circumstances many hospitals will be antagonistic. The organizations already mentioned have done most creditable work and the American College of Physicians, by co-operating with them in what already has been done, doubtless can

prove of service. However, no organization has, as yet, surveyed our hospitals with regard to the proper handling of non-surgical patients from the standpoint of how the internists consider these patients should be handled. In fact, the programs for management and efficiency which have been proposed to our hospitals have been instituted as blanket schemes for management and such schemes have emanated largely from a surgical group or from a lay or office working group not intimately aware of the needs of the internist. Thus it follows, commonly, that in the working out of plans proposed, most hospitals are surgically "top heavy." To be sure, the internist is a member of the staff and is held responsible for the type of work which he carries on, but he is not given a position to carry on his work along lines which he may think desirable. Rather, he is compelled to fit himself into a scheme which frequently enough does not suit his requirements or which is not what he considers the best that might be devised.

From communications which have frequently come to me, I gather that the internist is not satisfied with the position of subordination to which he is subjected in the vast majority of our hospitals by the workings of so-called standardization plans as they now exist. Frequently enough, he is not consulted with respect to staff members, equipment, laboratory personnel, laboratory procedures, autopsies, staff meetings or records. It is not to be wondered that such internist is not an enthusiastic staff member, does not support the monthly clinical conferences and takes relatively little interest in inter-departmental activities. Your committee has endeavored to find some way in which the College could help. Co-operation with already existing organizations concerned with hospital management and practice has been offered, but in no instances has this co-operation been proffered along lines which would make the endeavor, so far as the College were concerned, co-operative along lines of equality.

At present, it is the sentiment of your committee that the College should in no way hamper the hospital activities of sister organizations but should not accept in these activities a subordinate position. Your committee feels, that without great expense in each state or province, the hospital situation with respect to the internist can be canvassed through the supervision of one of your Fellows, most appropriately the Governor of the College for the State and by this means within a reasonable period of time, the College could be aware of what actually is needed. Each Fellow would have to play his part in this activity and if supplied with suitable direction and comprehensive forms upon which to record observations, in due time information of great value could be collected. From these original sources, your committee and the Regents would be in position to propose a simple and definite plan whereby the defects existing in our hospitals today satisfactorily could be remedied.

The question of College activities for the Fellows generally, between annual sessions, repeatedly has been brought to the attention of your Regents and officers. There has been a

desire expressed by many that the College institute and supervise short-session, sectional, clinical conferences to be attended by Fellows located in groups of conveniently adjacent states or provinces. It has been felt that these gatherings would do much to stimulate clinical and scientific medicine and, from such sessions, the hospital needs of the various communities accurately could be appraised. Further, these sectional meetings would indicate to the hospitals and the communities in which they are situated, that in the field of medicine, generally, there actually does exist a group other than the surgical. It is only by making hospitals and communities, what I might call "internist conscious," that our influence and our organization will become potent and direct.

I feel that during the coming year, definite steps should be directed toward arranging a program for at least mid-session gatherings of internists and these gatherings should be sponored by the College. It should be known in the various communities that they *are* sponsored by the College and in all instances the sessions should be attended by such officers, regents and governors as are available. The institution of sectional meetings and the direct canvass in each locality of the medical facilities of hospitals will prove too great a task for the home office adequately to bear. Consequently, it is the opinion of your retiring President that in the very near future, the College should have available to further the local and national interest of its Fellows, a full-time, paid, medical man, not a practitioner, but thoroughly experienced, who would serve as a field secretary. Only in this way is it, in my opinion, possible for the College to extend its influence in communities, to know the needs of medical men in a medical way, to accumulate data for your officers, regents and general headquarters, which will be reliable and complete. The time has come when the usefulness of a medical, field-secretary can be demonstrated to every Fellow of the College in a manner which is practical, and along lines for which there is need. I earnestly hope that those who have been entrusted with the responsibility for furthering the interest of the *average Fellow* in the *average* community of this country and Canada, will see to it that, without delay, there is supplied the field-secretary for whom I can see so great a need.

Finally, it is a pleasure for me to express to you the privilege which you have given me for so long a time to work among you and to thank the Fellows, officers and regents for the co-operation which they have given me in my efforts to build the College along lines which will be substantial and permanent. It has been a great satisfaction intimately to come into relationship with so great a number of internists and laboratory workers on the American continent. This personal contact has been extremely broadening. It has been a potent influence toward counteracting whatever pessimism I may have had with regard to the practice of internal medicine. I have found, in all sections of the continent, that internists were ethically and morally sound; they were good cit-

izens, they were gentlemen; some of them were prosperous. But the greatest inspiration has come from the observation of how universally well the internist was practising his art. One who has confined himself only to office and laboratory practice in the great medical centers, can have no appreciation of what is being accomplished by internists in communities of smaller size and influence, unless, as fortunately has been my lot, he is able to see for himself how, in other communities, the daily work in office and hospital is carried on. Frequently, in the most unexpected places, I have had opportunity of observing a type of work of the most superior kind, in fact, work of such excellence that, if it were done in connection with one of our larger institutions, would bring to the physician a reward both scientific and practical. I feel that the American College of Physicians has been an influence in stimulating throughout the land among many internists the daily performance of duty along highly commendable lines. It is my opinion that the influence of the College in this regard has only begun. But it *has* begun and I regard it a great achievement to have made available to internists an organization for their own expression, for their betterment, and to stimulate them to greater accomplishment. But, lastly and best of all, in the banding together of internists throughout the Americas, there has followed, through the College, the development of a spirit of individual and group loyalty, of scientific, honest and sportsmanlike conduct which bespeaks great advances, social, professional and scientific, in the not distant future.

Adaptation and Compensation as Origin of Disorders*

By Julius Bauer, M.D., *Professor of Internal Medicine at the University of Vienna, Austria*

Mr. President, Ladies and Gentlemen, I appreciate highly the great honor of having been invited by the Board of Regents of the "American College of Physicians" to read a paper at this annual meeting and I am deeply indebted for having this opportunity. To a research worker and medical teacher it is the greatest satisfaction to see his work recognized and to get in personal contact with many representatives of the profession, in order to communicate them some of this work. But there is a slight difficulty. One's own research work must necessarily deal with a more or less limited, narrow field of medicine and I could not possibly hold the interest of all the members of the College if I spoke on a special problem of the many ones which have fascinated me for many years.

Therefore I thought to review with you a greater number of pathological conditions in order to throw some light upon them from the general biological and special points of view. Sometimes it is more interesting to reveal a new side of an old and well known thing than to get acquainted with new things.

We are fascinated every day at the patient's bedside and in the dissecting-room by the marvelous functional and anatomical changes of an organism induced by a primary lesion or disturbance of an organ showing the character of adaptation or compensation. This term includes the conception of usefulness of these changes and bears upon each process which tends towards healing of the primary lesion. But this teleological conception in accordance with and innate to the human mind prevents us frequently from detecting a more complicated mechanism and from becoming aware of the fact that we have to pay for the originally useful adaptative process. We have to pay either on account of some accidental or obligatory by-effects of this process or on account of its exaggerated intensity. The original usefulness of the adaptation recedes entirely in the background and the adaptative or compensatory character of the present pathological condition is scarcely to be revealed. Quite a great number of disorders are to be attributed either to some undesirable and fateful by-effects or to an exuberance of adaptative processes.

*Lecture delivered before the American College of Physicians, March 5, 1928, New Orleans, La.

Arterial hypertension in a case of nephritis may certainly be useful and facilitate the excretion of urine. The higher the pressure in the renal arteries the better the filtration process in the glomeruli. We do not yet know the actual mechanism of the genesis of such a renal hypertension but we may call it adaptative because of its apparent usefulness. But this adaptative process involves the obvious unpleasantness and the danger of an arterial hypertension. The patient may be saved from a renal insufficiency but he may suffer from headache, dizziness, aortalgia and all the other well-known consequences of arterial hypertension and may even die from apoplexy or cardiac insufficiency. The development of vicarious emphysema of one lung in a case of destruction of the other lung is without any doubt a compensatory process because it enlarges the respiratory surface through the distension of the alveoli. But such a permanent distension of the alveoli is easily followed by a destruction of the septa with a subsequent diminution of the capillaries. This renders the pulmonary circulation more difficult and requires a greater effort of the right ventricle. An originally useful compensation has become a danger for the heart and may shorten the life of the patient through an insufficiency of the hypertrophied myocardium. It is a matter of scientific discussion why an hypertrophied heart muscle does not possess quite the same power of accommodation to an increased effort as a normal heart muscle. A discordance between the increased mass of the myocardium and the scarcely or not at all increased mass of the specific conductor system has been given as the reason for the latter. One took into consideration the proliferation of the fibrous tissue in the myocardium induced by the increased pressure upon the inner wall of the heart. At any rate it is obvious that an adaptative process as heart-hypertrophy in cases of valvular lesions or arterial hypertension involves at the same time a lowered functional accommodation and may herewith give rise to an insufficient heart function.

We owe to the Viennese clinician Wenckebach (1) the remarkable viewpoints concerning the interrelationship of advantageous and disadvantageous consequences of a cardiac insufficiency. He pointed out particularly how useful a congestion of the liver may be to the patient whose right ventricle became insufficient. As the liver is able to hold up to 1½ liters of blood like a sponge it relieves the cava inferior and subsequently the right heart of a considerable amount of blood, and prevents a stasis in the more peripheral part of the cava with a subsequent inundation of the tissues by edema. But such a patient with an adaptative liver congestion and therefore still sufficient heart action may complain of a pressure feeling in the right abdominal side or may become dyspeptic on account of a stasis in his portal circulation, particularly in his stomach. In cases of insufficient action of the left ventricle a stasis in the pulmonary circulation may even prove fatal by the danger of a lung edema, but only as long as the right ventricle

(1) K. F. Wenckebach, Med. Klinik, 1928. Nr. 1. p. 1.

works sufficiently and its output is not diminished, the patient is less dyspneic, tricle fails to discharge its whole contents the congestion in the lungs is diminished, the patient is less dyspnoic, he is not in the danger of suffocation any more but he has to pay for it with congestion of the liver and its consequences. Sometimes it happens that digitalis-treatment improving only the right ventricle in such a case is followed by a diminution of the liver congestion but at the same time there appears an increased dyspnea. In addition to that it is worth mentioning what Wenckebach (2) pointed out concerning the relief of the dreadful pain of an angina pectoris by a beginning insufficiency of the left ventricle. He gathered rather remarkable arguments in favor of the supposition that this pain is due to a distension of the aortic wall and coronary arteries through a constriction of peripheral arteries. This distension decreases as soon as the energy of the left ventricle is diminished. Whether this theory is accepted or not, we must perforce acknowledge the interesting old experience that a beginning insufficiency of the heart muscle stops a stenocardiac attack; that is to say it is an adaptative process referring to the attack, but this adaptation may be rather dangerous to the patient and cost him even his life. In cases of chronic heart insufficiency following attacks of angina pectoris digitalis treatment may improve the heart but will at times release those attacks anew (Wenckebach 2).

(2) K. F. Wenckebach, Wien. klin. Wochenschr. 1928. Nr. 1. p. 1.

When a case of renal insufficiency with a lowered power of water and salt elimination develops a general dropsy then this dropsy is to a certain extent an adaptative process for the kidney, but it may become fatal for the organism on account of different possibilities which arise from such a condition. It is a well known fact that an increased number of erythrocytes is not infrequently to be met with in cases of chronic cardiac insufficiency. The mechanism of such an erythrocytosis is still a matter of discussion, but doubtless we may consider it as an adaptative process in order to compensate for the deficient transport of oxygen-carriers by their increased amount. The same is true of the erythrocytosis in cases of chronic bronchitis with emphysema, where it compensates for the deficient reception of oxygen just as in high altitudes or under a low atmospheric pressure. But in cardiac cases as well as in cases of emphysema such a compensatory erythrocytosis is at the same time disadvantageous on account of the increased viscosity which makes the heart work more difficult.

We owe to the physiologists A. Fick and O. Frank the knowledge of the fact that the contractions of a muscle and especially of the heart muscle are up to a certain limit the more intensive and energetic the higher the initial tension, that is the filling of the heart, and the greater the load, that is the arterial pressure. This touches upon the riddle of the heart's accommodation and its reserve power. Therefore it is an adaptative process if a collapsed man's heart shows di-

minished contractions. Since the whole blood is filling the dilated blood vessels of the abdominal cavity; the physiological stimuli of the heart muscle, its tension by the contents and the peripheral blood pressure are markedly diminished. But this adaptative mechanism may cost the man's life, if the heart does not contract sufficiently to maintain the circulation. It is to a certain extent a sort of chronic collapse as Wenckebach (2) described in some cases of enteroptosis. The flabby abdominal wall, the insufficient action of the diaphragm and subsequently of "the abdominal press" brings about a permanent overfilling of the splanchnic blood vessels. Tachycardia, palpitation, general weakness and tendency to fainting are the consequences of such a condition and are at least partially due to an adaptative heart alteration.

Anemia is compensated by more frequent contractions of the heart, but the tachycardia may be a source of subjective disorders and is not without importance for the heart condition. We credit Yandell Henderson, Haggard (3) and their associates for having elucidated another compensatory process in cases of acute posthemorrhagic anemia. An increased air hunger and hyperpnea are well known compensatory symptoms after a hemorrhage and even a small loss of blood from the circulation induces a marked increase in the pulmonary ventilation. This sort of augmentation of the oxygen-intake is certainly useful as the number of oxygen-carriers is diminished. But Henderson taught us that this adaptative process involves at the same time a danger. First the vigorous breathing as a considerable muscular exertion requires additional oxygen which is wanting, and secondly it causes what he called acapnia. Excessive breathing ventilates off an abnormally large amount of carbon dioxid and leaves the blood abnormally alkaline. In compensation, alkali then begins to disappear from the blood and is carried away partially by the kidney, but most of it passes into the tissues to be stored there in a way not yet fully understood. It has been pointed out by Henderson (3) that it is chiefly this disturbance of the acid-alkali balance termed acapnia that may become fatal in exsanguination. In any case we have independently of theoretical explanations to acknowledge the statement that an originally useful, adaptative proces sas the hypernea after a hemorrhage brings about a disadvantageous by-effect.

(3) Y. Henderson and H. W. Haggard, Journ. of the Amer. Med. Assoc. 1922. vol. 78, p. 697.

Inflammation is generally spoken of as an adaptative process concentrating the defensive power of the organism upon a point exposed to the danger. But its consequences are usually the starting point of disorders. That holds true for the actual fight in the form of an acute or chronic inflammatory process as for the devastated and insufficiently restored battle-field in the form of a scar. It needs no further detailed explanation how far fever with its consequences for the organism, how far the production of inflammatory tissue of unspecific or specific character as a tubercle or gumma and

the development of shrinking, dragging or constricting scars represents the typical combination of an adaptative primarily useful process with disadvantageous by-effects of this very process. In certain organs a destruction and loss of parenchyma may be compensated by a powerful regeneration as it is to be observed in the liver. But even such a compensatory regeneration may be the origin of new disturbances. We learned through the investigations of the late Viennese pathologist Kretz that the regenerating liver tissue shows quite an irregular and disordered structure without normal relationship of blood-vessels and small biliary vessels. This discordance in the regeneration is the cause of a new nutritive damage of the regenerated parenchyma and initiates its degeneration as soon as it has been built up. A few years ago G. B. Gruber drew our attention to this automatic mechanism of regeneration and degeneration of the liver in cases of liver cirrhosis. From our point of view it is an interesting illustration of the insufficiency and incompleteness of an apparently compensatory process involving at the same time the source of new destruction and new disorder.

So far we have given some illustrations of unwished-for and fateful by-effects of adaptative and compensatory changes in the organism. In the following we shall try to demonstrate injuries and disorders due to exuberance of adaptative and compensatory processes. In spite of their frequency we should wonder at the usual precision of adaptative reactions determined exactly in their intensity by the releasing stimuli. The most common and striking instance is the anaphylactic hypersensitiveness. It plays an important role in the human pathology not only in the usually so-called allergic hypersensitive condition as asthma, urticaria, angioneurotic edema, eczema, gastrointestinal disturbances and perhaps migraine, but also in infectious diseases or in certain cases of rheumatism. Anaphylactic hypersensitiveness originates from the inherent ability of the organism to produce antibodies as a defence against heterogenous protein and probably also some other substances that are foreign and therefore not harmless for the body. Hypersensitiveness is the result of this certainly adaptative property, but it may dominate in many clinical pictures and illustrates sufficiently how an originally adaptative process creates different sorts of disorders by its useless exaggeration.

The mobilization of leukocytes in certain infectious conditions is an adaptative reaction of the organism making it easier to fight against the bacterial intruders. In exceptional cases this mobilization is exaggerated, the adaptative stimulation of the leukopoëtic system releases a hyperactivity of this system surpassing by far the demand of the organism and producing a pathological condition which we know as acute leukemia. This mechanism of a social and anarchistic independence of certain organs and functions released by an adequate, adaptative stimulation is not quite infrequently the origin of serious disorders particularly in endocrine pathology.

A hyperactivity of the thyroid gland for instance is considered as a useful

adaptative reaction in many infectious processes. Typhoid or acute rheumatic fever, dysentery and other bacterial conditions seem to be combatted more easily with the help of the thyroid gland. French authors go even so far as to recommend a thyroid treatment in refractory cases of acute rheumatic fever not showing any benefit from salicylate treatment or an increased volume of the thyroid gland. Experimental medicine supports this view to a certain extent as we have learned that all cellular activity including the production of antibodies is stimulated by the thyroid hormone. But how frequent are the cases of hyperthyroidism of all degrees up to the classical exophthalmic goiter appearing after such a fight against a bacterial infection! Certainly we find as a rule in those cases of exuberant adaptative reaction of the thyroid upon infections an explanation for this exuberance. Those individuals were disposed to an exaggerated thyroid hyperactivity and betrayed this individual disposition before the releasing infection by scarcely indicated rudimentary signs of hyperthyroidism, they always had been nervous and irritable, had a tendency to tachycardia and sparkling eyes, perhaps also a slight swelling of the thyroid, and their family history reveals some other members affected by thyroid hyperactivity. It may be also learned by personal observations that a great psychical shock just previous to the onset of the infectious disease was an additional etiological factor of the hyperthyroid condition, but the chief point is at all events the exuberance of an originally adaptative reaction. The thyroid does not obey any more its physiological regulatory mechanisms, it does not care for the thyroxin- requirement of the organism. If we look for focal infections in cases of hyperthyroidism in order to remove them we try to get rid of the primary releasing stimulus, but we do not succeed always as soon as the anarchistic independence of the thyroid has surpassed a certain limit.

The fearful but grandiose starvation experiment of the war showed that the thyroid as well as the gonads undergo a marked atrophy, manifest not only to the pathologist, but also to the clinician. But it is of the greatest interest from the aspect of adaptative mechanisms that this diminution of the thyroid activity in starvation is a useful condition saving energy and perhaps the life of the undernourished organism. One would not have expected that human beings can be maintained alive with such a minimum of food but one found that the basal metabolism of those starving individuals was markedly diminished without any doubt on account of the adaptative hypothyroidism. It is the very opposite of what we observe in overfed individuals and what is called luxury consumption and due to a hyperactivity of the thyroid gland, because of its disappearance after thyroidectomy (E. Graef). Everywhere in Central and Eastern Europe cases of hypothyroidism and myxedema were to be seen more frequently during the particularly bad time of food supply. But these cases were not the most starving and most endangered, they were apparently disposed to a hypofunction of the thy-

roid even before the undernourishment and fell ill as soon as the moderate insufficiency of food supply released an exaggerated adaptative inhibition of thyroid function. We have to add that the thyroid and gonadal atrophy in starving individuals is not purely a corresponding part of a general atrophy of the whole body, as we know that under the same conditions the suprarenal cortical tissue undergoes a marked hypertrophy (McCarrison). An analogous proliferation has been found recently in the Langerhans' islets of the pancreas (Jorns 4) and it agrees entirely with this

(4) G. Jorns, Deutsche med. Wochenschr. 1927. Nr. 32. p. 1339.

statement that the blood sugar of a starving person shows a marked diminution (M. Freund 5). Every ex-

(5) M. Freund, Zeitschr. f. physikal. Ther. 33, p. 133. 1927.

perienced physician knows the type of extremely stout people with symptoms of hyperthyroidism. It is unpleasant to meet with this clinical syndrome on account of the impossibility to apply a thyroid treatment in order to reduce the body weight. But we agree entirely with H. Zondek (6)

(6) H. Zondek, Klin. Wochenschr. 1927. Nr. 17.

who considers the hyperthyroidism as a compensatory process fighting against the obesity. We have only to add that such an exaggerated adaptative reaction may be more dangerous for the patient, than the primary releasing obesity.

If we see acromegaly appearing during and after a pregnancy or in addition to myxedema then we may also think of an exuberant compensation. Pregnancy as well as an insufficient thyroid function are adequate stimuli for the anterior lobe of the pituitary gland. I pointed out in 1917 (7) that a slight or moderate hyper-

(7) J. Bauer, Konstitut. Disposition zu inneren Krankheiten. Berlin, Julius Springer, 1917. 3d edition 1924.

thyroidism as well as a diminution of the gonadal activity seem to be useful adaptations of the organism in its fight against a tuberculosis. It would go too far to discuss here in detail the observations and arguments allowing this statement. But today it interests us that exceptional cases with a cured or at least successfully combatted tuberculosis had to pay for this good result with the consequences of an exaggerated adaptation and developed hyperthyroidism or had lost their gonadal activity.

Exaggerated compensation is finally to be taken into consideration also in cases of benign or malignant neoplasms. From the exuberating callus and the keloid we see transitions leading to some types of neoplastic conditions developed on the basis of an exuberant reparative process.

I think it needs no further enumeration of analogous pathological processes and disorders which may be attributed quite generally to a primary compensation and adaptation of an entirely different and even rather distant pathological event. What we have discussed seems to be quite sufficient in order to recognize the far-reaching significance of always the same principle and mechanism in the

production of functional or morphological disturbances. A thorough analysis of pathological conditions reveals not infrequently such a chain of primarily adaptative and compensatory reactions inducing various disorders either by their accidental by-effects or by their not sufficiently checked and regulated intensity.

In the beginning of this paper I mentioned that the term adaptation and compensation involves the teleological conception of something useful.

The true naturalist is always shocked at a teleological contemplation of natural processes. He likes to understand only the mechanism and its causation but holds his hands off from a supposed aim and purpose of this mechanism. But even a naturalist is always a human being and can not overwhelm his own human nature and mind, he is pleased with such a teleological consideration even if it surpasses the limits of his science. All the grandiose processes observed in clinical pathology and studied by the means of chemical, physical, anatomical, biological methods they reduce to a teleological contemplation beyond the real scientific basis. It is without any doubt an immanent characteristic of the human spirit not to describe only the hypertrophy of the overstrained heart muscle or of the left kidney after the removal of the other, not to study only the mechanism of the development of a collateral circulation after the obstruction of a blood-vessel, but to recognize the usefulness of such a reactive process for the organism and herewith its apparent aim.

It was the great Viennese clinician Nothnagel (8) who delivered an address, at the International Medical Congress in Rome in 1894 on the adaptation of the organism in pathological conditions and came to the conclusion that every apparently adaptative and compensatory process is originally aimless and is the natural consequence of the changed situation, of changed influences and stimuli. General physical, chemical and biological laws govern and regulate all these processes which as a rule appear to be, and are useful, indeed, but which are not always so in any case to be observed and which may be even disadvantageous in other cases. The varying requirement of the functional activity of an organ is able to regulate this activity and the varying activity has an influence upon the morphological structure of this organ. So we see regeneration, hypertrophy or atrophy of a parenchyma as the consequence of the organism's varying requirement of its special function. But why all these physical, chemical and biological laws provoke finally alterations of a regularily useful character, that is a question beyond the limits of the human mind. So far lead the conclusions of the pure mechanistic aspect of Nothnagels!

(8) H. Nothnagel, Wien. med. Wochenschr. 1894. Nr. 15.-19.

What we have pointed out here is an addition to this conception. Nothnagel had mentioned only some of the possible detriments caused by apparently adaptative processes. G. B. Gruber ()9

(9) G. B. Gruber, Münchn. med. Wochenschr. 1924. Nr. 38. p. 1316.

spoke of adaptative disease in order to emphasize the disadvantageous consequences of some adaptative structural changes of a parenchyma. We intended to demonstrate that the usefulness of apparently adaptative and compensatory processes is as a rule relative only to one special function and must be paid for by the organism. The fateful by-effects or the consequences of an exuberant compensatory reaction may rule the situation. The term compensation is no more correct and should no more be used in such a case. We see in pathology as everywhere in nature that the teleological aspect of usefulness is always the product of the human mind only and we have to be conscious of this statement. This holds true particularly for our therapeutic activity which has to support the useful spontaneous reactions of the organism and has to suppress their dangerous by-effects and to inhibit their exaggerations. Let us hope that future medicine will find out all the ways of doing so.

Multiple Myeloma*

By Davil P. Barr, M.D., *St. Louis*

ALTHOUGH the disease known as multiple myeloma has held a fascination for many observers, knowledge of its nature has progressed very slowly. During a period of more than seventy-five years, less than 200 authentic cases have been reported. It was recognized as early as 1848 when Henry Bence Jones saw with Sir James Watson a patient whose urine contained a strange protein which he described as the "hydrated deuteroxyd of albumin." Two years later, the clinical history of this same patient was detailed by McIntyre under the designation of mollities ossium. The association of multiple bone lesions with the unusual protein of Bence Jones was thus clearly established but 35 years passed before a second case was recorded. The paper by Kahler in 1889 offered the first adequate clinical description and marked the beginning of the accumulation of authentic cases. The condition is sometimes known as Kahler's Disease.

During the past three years, it has been our good fortune to see several cases of multiple myeloma. Time permits us today to consider only one, a case which, however, may illustrate some of the difficulties of diagnosis and of classification. Before presenting the case, it may not be superfluous to detail some of the more striking features of multiple myeloma. It is admirably defined by Ewing as a specific malignant tumor of the bone marrow arising, probably, from a single cell type and characterized chiefly by multiple foci of origin, a uniform and specific structure composed of plasma cells or their derivatives, rare metastasis, albumosuria and a fatal termination. Any bone may be involved but the ribs and sternum suffer most often while vertebrae, skull, femur and humerus are less frequent sites. Although the lesion is always primary in the bone marrow, the cortex may suffer active absorption. Extension through the periosteum and the surrounding tissue is not common.

Pain is the most constant symptom. It is often excruciating and may occur wherever bones are effected. It is frequently diagnosed as neuritis, lumbago, pleurisy, sciatica or sacro-iliac strain. It may even be mistaken for osteomyelitis, a diagnosis rendered not unlikely by the intermittent and occasionally high temperature which may accompany the disease. Skeletal fractures from most trivial

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causes are frequent. The nutrition of the patient may be long maintained but as the end approaches extreme emaciation is the rule. There is often a marked secondary anemia. Bence Jones protein, perhaps the most widely known feature of the disease, has been reported in only about 40 per cent of cases. While this low figure is due in large part to the inclusion of cases in which the test was not done, it is nevertheless true, that albumose may in certain cases be persistently absent. In the carefully studied series of the Mayo clinic it was found in 80 per cent of the cases.

The patient whom we shall report today was a salesman for a refrigerator company, 49 years of age, who entered Barnes Hospital on May 12, 1927, complaining of severe pain in his right lower chest and in the right hip and thigh. Four months before, in the early part of January, he had contracted a distressing cough which was followed a week later by a sharp pain in the chest. The cough persisted until the end of January when he was forced to go to bed. At this time he had a high fever, more violent pain in the chest as well as general aching. His condition was diagnosed as influenza. He was taken to a reputable hospital where he was told that a rib had been fractured. There followed a period during which he attempted to continue his work as traveling salesman. The pain in his chest was constant and distressing. He sought medical advice in Philadelphia and in New York. Finding no relief he returned to St. Louis but soon left for more trips East and South. He saw several physicians. He was treated for "neuritis," for fractured rib." His last physician after repeated X-ray pictures told him that his chest was not affected but that he probably had cancer of the prostate. The pain in the right hip and thigh started only a week before admission and followed a fit of laughter. The pain was excruciating and kept him from moving his leg. It was the immediate cause of his admission to the Hospital. Nothing in his family history or in his antecedents seemed to be relevant to this trouble. Examination revealed the appearance of chronic illness and the effect of prolonged pain. Although the man had lost 20 pounds in four months he did not look particularly ill-nourished. On the sixth and seventh rib near the costo-chondral junction nodules about one inch in diameter could be easily palpated. A larger nodule could be felt in the eighth rib at the costo-chondral junction and another on the ninth rib. The abdomen was held with considerable rigidity. Percussion of the liver indicated a border two fingers below the costal margin. The spleen could not be palpated. Motion of the hip, when sudden, caused exquisite pain. By care, however, it was possible to flex and to extend both the leg and the thigh. There was no localized tenderness in the pelvis or leg.

The story of prostatic involvment led to a very careful examination with negative results. Other places likely to cause osseous metastasis, the breasts, the thyroid and the kidney regions, were searched in vain. The urine showed a trace of albumin, with hyaline, granular and cellular casts. Bence Jones protein was found in

large amounts varying on different examination between 2.5 and 8 grams. There was a marked secondary anemia, with 2,500,000 red blood cells and 37 percent of hemoglobin. The white blood cell count was most interesting, 10,200 leucocytes were found. An extremely careful differential examination revealed only 42 percent of polymorphonuclear neutrophiles, and 16 percent lymphocytes, but 17 percent of myelocytes, and 6 percent of myeloblasts. During the count five megloblasts and one normoblast was seen. Some cells which resembled plasma cells were seen.

X-ray examinations showed numerous dark, punched-out areas in many bones with localizations in the ribs, humerus, vertebrae and skull. The patient was told that he had a serious disease of the bones and that any slight indiscretion in lifting or any strain might cause a fracture. He was particularly cautioned to be careful of his right arm, in the humerus of which was seen a large rarefied area. Shortly after his admission, there occurred an accident so characteristic that it may perhaps be recited. A telephone call came for the patient. The nurse handed him the telephone from the bedside table, telling him that he could leave it in his bed when he finished and that she would place it back on the table for him. A slight delay occurred. The patient becoming restless placed the telephone back on the table with his right arm. The act was accompanied by a frightful pain in the middle of his arm where a fracture was later found. This accident had a most unfortunate effect on the patient's morale. Following it he ate poorly, lost weight rapidly, until on July 8th when he finally died he presented a most extreme emaciation. Only one development of importance was observed. His white cell count increased to 21,000 and the high percentage of myelocytes remained almost unchanged. The autopsy revealed in addition to the extreme emaciation, masses and fractures of five of the ribs, a large nodule on the left humerus, a complete fracture of the right humerus, rarefactions of the skull, metastases to the liver and to both kidneys. The microscopic examination showed that the tumors in the bones were composed of cells of the plasma-cell type, together with abnormal forms of multinucleated cells.

The lantern slides may be instructive and illustrate some of the chief features of the case.

(1) The first represents an X-ray picture of the thorax. Careful inspection reveals a number of tumors and fractures. Close to the angle of the right scapula may be seen a large bulging tumor. The third rib shows for several inches almost complete absorption.

(2) The second slide shows the characteristic lesion of the skull with the sharp punched-out edges of the tumors.

(3) The next slide shows the original appearance of the right humerus. It was this picture which induced us to tell the patient that he was in imminent danger of breaking his right arm.

(4) The next slide shows a pic-

ture taken shortly after the fracture had occurred. As in many cases of pathological fracture the presence of tumor tissue tends to hold the bones in correct position. In this instance the displacement is very slight. The interne who saw the patient immediately after the accident, tried to obtain crepitus or signs of displacement and failing to find these signs he thought that the arm was not broken. It was only the continuance of excruciating pain which led to the X-ray examination and to the splinting of the arm. It is also interesting that attempts to set the arm resulted only in increasing the displacement.

(5) The next slide shows the condition found at autopsy, the over riding, the displacement of fragments, the non-union and the beginning of callus formation. In this picture also one can see the extent of involvment, the large tumor masses and the erosion of the cortex.

(6) The next slide presents a microscopic picture of the tumor cells. This particular section was taken from one of the rib tumors and shows the plasma cells closely packed, surrounding one of the large multinucleated cells which were characteristically found in all of the lesions.

(7) The next slide is a much higher power, showing the general character of the cells.

(8) The next slide shows the plasma cells infiltrating the tissues about the kidney tubules. In no place were there gross tumors in the kidneys. The infiltration, however, was dense and extensive and involved the interstitial tissue just beneath the cortex.

(9) The last slide shows the extensive infiltration of the sinusoids of the liver.

Consideration of this case suggests several interesting questions. Early descriptions of myeloma and, indeed, some later ones considered it to be a disease strictly localized to the bone marrow. Differentiation from other tumors was often made on this basis. As case reports accumulated, it was found that, under certain circumstances, the cortex of bone might be eroded. Local extensions into surrounding tissues were described. Later cell accumulations similar to those of the bone marrow were discovered in the liver and spleen. This did not seem so extraordinary in a disease which, by definition, involves blood producting tissue. It is well known that in fetal life, liver and spleen have properties of blood formation. By many, these infiltrations have been regarded simply as extensions into the blood forming tissue of the internal organs. This conception, however, can no longer suffice. Reports have gradually accumulated concerning cases in which the invasion was not limited to the hematopoetic organs. In Frankl's case there was involvement of one adrenal gland and one ovary, as well as both kidneys. Schultz found infiltration of a tonsil. Verebely found a plasma cell tumor in the tissue about the cricoid cartilage. In three of our own cases there have been involvement of the internal organs. In one of these, a unique case which has not yet been reported, we have found wide-

spread involvement of both lungs with the production of a pulmonary and subcutaneous emphysema. Possibly the most extensive spread of multiple myeloma occurred in a case reported by Nichol in a recent number of the Canadian Medical Association Journal. The tumors of bone, in his case, were typical. Bence-Jones protein was present. The metastases included the interstitial substance of the heart, the pleurae, the pancreas, the ovary, even the Peyer's patches of the intestines and the mesenteric lymph nodes. There were, as in one of our cases, multiple nodules in the skin. The present evidence, seems to indicate that multiple myeloma may be a general disease, arising no doubt in bone marrow but involving in its course many other organs. The manner of these distant involvements resembles less the ordinary metastasis than the cellular infiltration of the leukemias.

In this connection, it may be of interest to inquire how far the comparison between multiple myeloma and the leukemias may be carried. It is often stated that in myeloma, a normal blood count is found. In our case, there is a leucocytosis with a great number of myelocytes and many myeloblasts. While this is not usual it is by no means an isolated observation. Myelocytes have been reported in other cases. In one instance these cells constituted 25 percent of the total. Plasma cells have also been demonstrated in the circulation. It might be mentioned that this represents simply an extension of abnormal cells from the diseased bone marrow. A suggestion which gains force when it is remembered that very occasionally a leukemic blood picture has been seen in metastatic carcinoma of the bones. The similarity between the two conditions, however, does not entirely end with the blood picture. The so-called metastases of myeloma may be more accurately described as "infiltration" and resemble closely both in distribution and character the infiltrations of leukemia. Thus they are found more commonly in the liver and the spleen but may involve the kidneys, the skin and many other organs. The bone marrow ordinarily appears quite different in the two conditions. Tumors are undoubtedly rare in leukemia.

In the case of Moore, which was reported from our Hospital, there were, however, multiple bone tumors resembling most closely multiple myelomata. The clinical picture was that of myelogenous leukemia and the white blood cells at one time numbered 300,000. It is true also that in certain unusual cases of myeloma the involvement of bone marrow may be as diffuse as in typical leukemia. As an additional point of similarity, it is interesting to recall that in the case of leukemia reported by Askanazi, Bence Jones protein was found in the urine.

In this short paper it is not desired to advance a thesis that leukemia and myeloma are different expressions of the same disease. It may, however, be not entirely superfluous to emphasize that in the light of more recent reports their similarity is often most suggestive.

Summary

1. A case of well-established multiple myeloma (Kahler's disease) has been reported.

2. This was found at autopsy to present evidence of extensive involvement of liver and kidneys. It showed during the entire time of observation a leukemic blood picture.

3. These observations are in accord with recent reports in the literature which seem to indicate that myeloma is not confined to the bone-marrow but may be a systemic disease with generalized manifestations. Also that the similarity of multiple myeloma and leukemia is much more striking than was formerly thought.

4. The case reports of multiple myeloma have not been sufficiently numerous to bring out all the points of its natural history and further observations of its general character, its metastatic qualities and its relation to the leukemias are needed.

Studies in Blood Volume with the Dye Method*

By Leonard G. Rowntree, M.D., and George E. Brown, M.D., *Division of Medicine, Mayo Clinic and the Mayo Foundation, Rochester, Minnesota*

NEW conceptions concerning blood are urgently needed in medicine, since the routine count of blood cells and the determination of the hemoglobin relate entirely to the concentration of the blood and are in no way related to the important problem of blood quantum. During the last fifteen years we have learned much from the accumulated evidence of studies of blood and plasma volume with the dye method. The results of these studies are now being assembled in monograph form. In this report, we shall present only a brief synopsis of some of our observations in this important but neglected field.

The dye method of determining plasma and blood volume was introduced in 1915 by Keith, Rowntree and Geraghty. The method involved a new principle: the direct introduction into the circulation of a known amount of a nontoxic, slowly absorbable dye which remains in the plasma long enough to mix thoroughly and to permit the determination of its concentration in the plasma colorimetrically by comparison with a suitable standard mixture of dye and serum. The extent of the dilution of the dye determines the plasma volume. The total blood volume is computed, utilizing for the purpose the hematocrit values obtained after rapid and complete centrifugalization.

It was shown that for normal man the plasma volume was approximately 5 per cent of the body weight (a variation of from 40 to 60 c.c. for each kilogram) and the total blood volume 8.8 per cent of body weight (a variation of from 70 to 100 c.c. for each kilogram). Duplicate determinations on normal subjects yielded approximately identical values. Decreased volume following rapid bleeding and increased volume immediately incident to infusion by sodium chloride solution were fairly accurately reflected by this method. Increased volume relative to body weight for blood and plasma were encountered in the late stages of pregnancy and decreased volume in obesity. Changes in blood volume did not appear to bear any significant relationship to hypertension.

During the last decade the method has been employed by numerous investigators both clinically and in animal experimentation, and it has been subjected to rather searching criticism. Certain steps in the method have been questioned and changes in technic suggested. Other substances, dyes, or

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colloids have been advocated as substitutes for vital red, but the original dye appears to have survived. As a matter of fact, the dye method appears to constitute the most practical clinical procedure now in use for determining the circulating plasma and blood volume. One explanation of this status of the method is that the carbon monoxide method, its only true competitor in the practical clinical determination of blood volume, has also been subjected to criticism. We have carefully considered the claims made for the latter method, and the criticism against it by various workers and can see no good reason for combining it with the dye method as has been suggested. In fact, after many years of experience with the dye method, in which approximately 1,000 volume determinations have been made on several hundred persons in health and disease, we find it sufficient for clinical needs. The particular objections that have been made to the method refer largely to blood volume; all workers concede that it furnishes the most accurate information available concerning plasma volume.

The objections which have been made to the dye method may be listed as: (1) lack of availability of vital red, (2) adsorption of dye by the blood cells, (3) variations in the time of mixing, (4) uneven distribution of blood and plasma in the body, (5) the fact that exercise is essential to proper mixing of dye in the blood, (6) indicator properties of Congo-red, (7) untrustworthiness of hematocrit data, (8) attendant dangers, and (9) the shrinkage of red blood cells resulting from the use of dry oxalate.

The various objections have all been subjected to careful consideration and to controlled experimentation. As a result we believe that all but the first and the last may be disregarded. Congo-red serves as an excellent substitute for vital red. The shrinkage in the cells incident to the use of dry oxalate as an anticoagulant averages approximately 3.4 per cent and can be readily adjusted by a change in the technic or by making the necessary correction. Our views in regard to these objections may be summarized as follows: We believe that vital red is entirely satisfactory for the determination of blood volume. It is nontoxic, nonirritant locally, and is adequate from the standpoint of slow absorbability and of tinctorial properties. It is not, however, generally available, hence, a substitute is desirable. According to Harris Congo-red has proved equally satisfactory in several hundred determinations. Many other dyes have been suggested, and there will doubtless still be others for, as we have advocated, any dye combining certain properties will probably answer the purpose. Corroboration of this is found in the work of Evans and Whipple, who used about thirty dyes, all of which yielded values for blood volume of the same order of magnitude. Colloids other than dyes may likewise suffice as evidenced by the work carried out with gum acacia.

Because of Lindhard's criticism of Congo-red as a substitute it has been subjected to control experimentation. In the concentrations used in the test there is no evidence of significant adsorption of Congo-red by the red blood cells. Variations in the dye

probably explain Lindhard's results. Neither was Congo-red detrimental because of its properties as an indicator since variation in color does not affect the method as employed. Our determinations throughout concern basal blood volume from determinations made in the morning following sleep, and with the patient at rest. If it is true, as has been suggested, that blood volume is affected by exercise, then we are faced by a new problem: the quantitative effects of exercise. However, Whipple in his study of this problem in dogs found that "no maintained or constant effects on plasma volume could be demonstrated." The opinion of Lindhard that blood volume values are acceptable only during and immediately after exercise is not borne out by our studies. For the dye method Lindhard advocates vital red as the most satisfactory test substance. Because of difficulty in obtaining this dye, we are utilizing Congo-red, and find it a satisfactory substitute.

The determination of blood volume should be made from three to six minutes after the injection of the drug. Much discussion has centered on the question of mixing curves and the most propitious time for making the determination. Two factors must be kept in mind: the thorough distribution of the dye throughout the body, and the collection of the blood-dye mixture prior to any great loss of the dye from the plasma. A consideration of the evidence the literature afforded, with the results of our own statistical observations on the mixing curves obtained in a large series of cases, did not disclose evidence that would change our original opinion, and hence we see no reason for departure from the technic as originally outlined.

Uneven distribution of red blood cells in plasma in different vessels has not, we believe, been proved to be a serious source of error in the method. Since, in our routine work, the dye has been injected into the veins of one arm and collected from the veins of the other, our results are at least comparable. In a certain series of cases blood was collected simultaneously from the veins of both arms with practically identical results. The technical and mechanical difficulties of repeating Lindhard's attempt to collect blood from the veins of the feet are, we believe, sufficient to vitiate the results of the test and to explain in part if not in full, his discordant results.

The hematocrit values as obtained by the method are not subject to great inaccuracy. The mean variation from the average value in each of 133 quadruplicate determinations was 1.5 per cent of the total blood in the hematocrit tube, which for a practical biologic test cannot be considered excessive.

Whipple's criticism of our technic relative to the shrinkage of red cells resulting from the employment of dry oxalate as an anticoagulant, is basically sound. He claimed that in a large series of determinations by the dry method and by his method, which involves the use of 2 c.c. of 1.6 per cent solution of sodium oxalate for 10 c.c. of blood, showed a discrepancy of practically 3 per cent. Control experiments which utilize heparin intravitally also show that the wet sodium oxalate method yields more accurate results. We are, therefore, accepting

Whipple's criticism and are making the necessary correction.

The dye method is entirely safe. We can see no justification for the fear of toxicity. During the course of five years we have not seen an untoward effect from the employment of the method in hundreds of determinations in practically all types of disease. The unfavorable results recorded would seem to be due either to unsatisfactory dyes or to faulty intravenous technic.

Blood volume may be correlated satisfactorily with body weight or body surface. Dreyer has claimed that it is a function of body surface. This is substantiated by a statistical consideration of our estimations for men and women of approximately normal body fluid. While from a scientific point of view blood volume probably should be expressed in terms of surface area, in practice values expressed in terms of weight appear to have approximately the same significance. The results of our studies are expressed both in terms of body weight and of body surface. Clinically, no advantage will accrue in the conversion of volume of blood to weight of blood unless such conversion is based on actual specific gravity determinations.

The normal values for plasma and blood volume have been determined in fifty healthy adults (preponderantly males) most of whom were men and physicians of the staff or laboratory assistants. The mean normal blood values with their probable error are as follows:

Plasma volume { 50 = 0.5 c.c. for each kilogram of body weight; 1929 = 53 c.c. for each square meter of body surface

Blood volume { 89 = 0.6 c.c. for each kilogram of body weight; 3383 = 33 c.c. for each square meter of body surface

Cells by hematocrit 42.1 = 0.3
Hemoglobin 16.6 = 0.2 gm. per cent

It would appear, therefore, that the blood volume by this method represents approximately one-eleventh of the body weight instead of the traditional one-thirteenth established by Welcker. The plasma accounts for one-twentieth of the body weight. A man of 70 kg. has slightly more than 6 liters of blood and 3.5 liters of plasma. These figures represent mean values. The range of normal is, of course, also important. It shows considerable latitude as:

Plasma volume { from 40 to 60 c.c. for each kilogram in 95 per cent of cases; from 1600 to 2400 c.c. for each square meter in 97 per cent of cases

Blood volume { from 80 to 100 c.c. for each kilogram in 86 per cent of cases; from 3000 to 3800 c.c. for each square meter in 88 per cent of cases

The question might be asked legitimately: Why are there variations of this magnitude in health? It cannot be answered completely at present because of lack of exact data. However, it is not excessive if compared with the range of variation in the erythrocyte count and hemoglobin values or the basal metabolism of normal persons. In seeking an explanation, how-

ever, certain factors might well be considered: (1) normal subjects show a wide range of deviation from the mean standard weight for age and height; the variations are not sufficient to classify as obese or definitely underweight; (2) age is important in the first three years of life; information is lacking with regard to subjects in the later decades; (3) certain variations in the cell volume have been noted with regard to sex; (4) rest and exercise; (5) environmental temperatures, seasonal and geographic variations; (6) diet, and (7) body temperature. Only the influence of the first factor has been adequately studied in our series. Further studies are necessary to determine the exact effects of the other factors on the volume of the blood and plasma. The mean values for the strictly standard weight group for age and height and the deviations resulting from underweight and overweight "normal" subjects are as follows:

Plasma volume	Standard weight 51.3 c.c. for each kilogram, 1979 c.c. for each square meter
	Underweight 53.0 c.c. for each kilogram, 1915 c.c. for each square meter
	Overweight 46.0 c.c. for each kilogram, 1992 c.c. for each square meter
Blood volume	Standard weight 88.7 c.c. for each kilogram, 3461 c.c. for each square meter
	Underweight 91.8 c.c. for each kilogram, 3273 c.c. for each square meter
	Overweight 78.6 c.c. for each kilogram, 3261 c.c. for each square meter

The standard group were all within 10 per cent of the accepted weight for height and age while the substandard groups represented healthy persons with variations in excess of a 10 per cent from the strictly normal range, but they were neither emaciated nor obese. The differences in body build in healthy persons have considerable effect on the plasma and blood volumes on the basis of weight, but according to surface area the relative values are more constant, especially in plasma volume.

$\frac{\text{volume}}{\text{surface area}}$ It is apparent, therefore, that several factors must be taken into consideration in interpreting volume changes in health and in disease. Incidentally, so far as body build is concerned, blood and plasma volume are essentially functions of body surface.

Repeated determinations on nineteen normal subjects at intervals of from two weeks to seventeen months showed fairly stable values for the blood and plasma for the same person. Some variations are noted, but in eight instances the changes were less than 5 per cent and in nine others they did not exceed 10 per cent. This leads us to believe that blood and plasma fluctuate somewhat from time to time but within narrow limits. The consisently high and low values respectively in certain persons seemed to increase materially our confidence in this method.

Nomenclature

In the beginning of our work the lack of a suitable nomenclature for blood volume states materially increased the difficulty of interpretation

and presentation of results. So serious was this difficulty that we were impelled to create new terms in order to meet the situation. The following was suggested: "normovolemia" to indicate normal volume, "hypovolemia" to indicate small volume, and "hypervolemia" to indicate increased volume.

Obviously the ratio of cell volume to plasma volume is important and should be recognized in any new terminology, hence the term "simple" to represent the normal ratio, "oligocythemia" to indicate decreased cell to plasma volume, and "polycythemia" to indicate increased cell to plasma volume. These three possible relationships apply equally well to normal, increased or decreased volumes of blood, thus we have the nine volume states which are indicated in Figure 1.

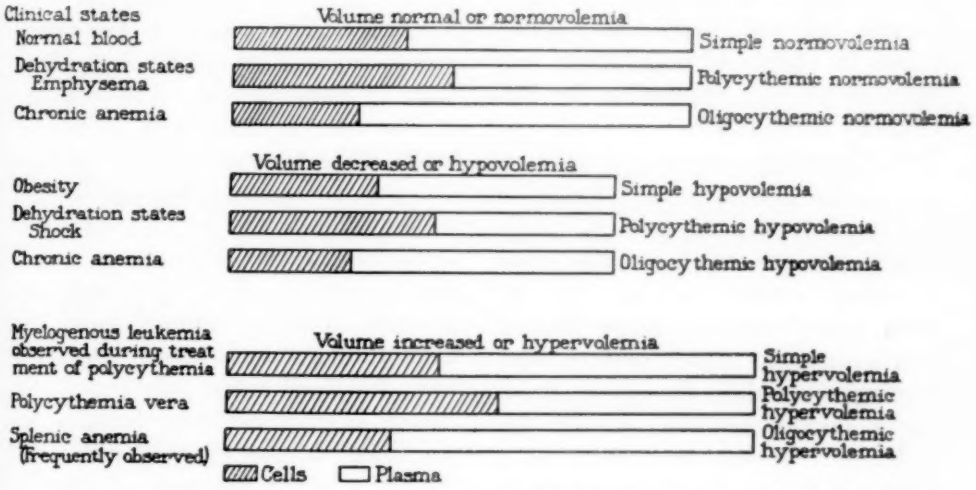

FIG. 1. Diagrammatic representation of possible blood volume states with different cell to plasma relationships.

CLINICAL DATA

From the preceding it might appear that these studies are of considerable academic interest but of little clinical significance in actual practice. This, however, is not the case. The material thus far presented (a study of more than 250 patients) constitutes an essential background to the proper understanding of our results in the application of studies of blood and plasma volume in clinical medicine.

OBESITY

Twenty-seven cases of obese patients have been studied. The mean weight was 106 kg., the mean increase in weight for the group over the normal mean weight was 56 per cent. This was accompanied by an increase of only 14 per cent in surface area, of 15 per cent in plasma volume, and of 9 per cent in blood volume. Obviously the increase in volume of blood and plasma correlates better with the increase in surface area than with the increase in weight.

The obese patient (106 kg.) has approximately 500 c.c. more blood than

normal. For each kilogram of weight the blood volume has diminished from 89 to 61 c.c. and the plasma from 50 to 36 c.c. Fat obviously has a very poor blood supply. The increase in weight, although enormous, is due to fat and is not accompanied by a significant increase in blood or plasma. Increase in the volume of blood so often alleged to be the cause of cardiac hypertrophy and myocardial insufficiency in obesity is nonexistent, and hence in no way responsible for this frequent complication.

The percentage distribution of blood and plasma volume to body weight in normal and obese subjects is shown in Figure 2. Overlapping of the curves is almost entirely lacking. On the other hand, if the percentage distribution is compared to body surface, overlapping is striking, the curves showing a decided tendency to correlate (Fig. 3). Hence, in obesity, as in basal metabolism, blood volume should be considered in relation to surface area rather than to weight.

The data relating to obesity and to the new-born infant furnish the most significant basis for considering volume relation to surface area rather than to weight. In adult subjects of normal weight, and in patients suffering from most diseases it is not a matter of so great importance.

Edema

The volume of blood and plasma has been carefully studied in a series of thirty-four cases of different types of edema. Obviously in order to obtain data of value it is necessary to consider blood volume values in relation to the body weight excluding the weight due to edema. This has been attempted in all cases, the normal weight being that prior to the onset of edema or the weight following edema. On this basis the following facts were noted:

The blood picture in glomerular nephritis is entirely different from that in nephrosis. In glomerular nephritis the blood volume is low with a mean value of 75 c.c. for each kilogram of body weight. The plasma volume, on the other hand, is unaffected. The decrease in blood volume is due to an absolute decrease in the volume of cells and indicates true or actual anemia; this is disturbing to the older conception that the anemia in nephritis is due to dilution from increased amounts of plasma. In contrast, the blood volume picture of nephrosis is of a moderate increase in the blood volume of both cells and plasma. In the presence of anemia there is a decided increase in plasma volume, an average of 70 c.c. for each kilogram instead of 51 c.c. noted in five cases of nephrosis without anemia. In the edema of glomerular nephritis erythrocytes are lost and little or no attempt is made to maintain volume by substitution of plasma. On the other hand, the restoration of plasma volume is complete in the case of nephrosis with anemia. Dilution of the blood suggests a possible mechanism for the production of edema and of anemia in the latter.

Cardiac edema is accompanied by blood volume changes simulating those described by Bolton in experimental passive congestion, namely an increase in both blood volume and cell volume,

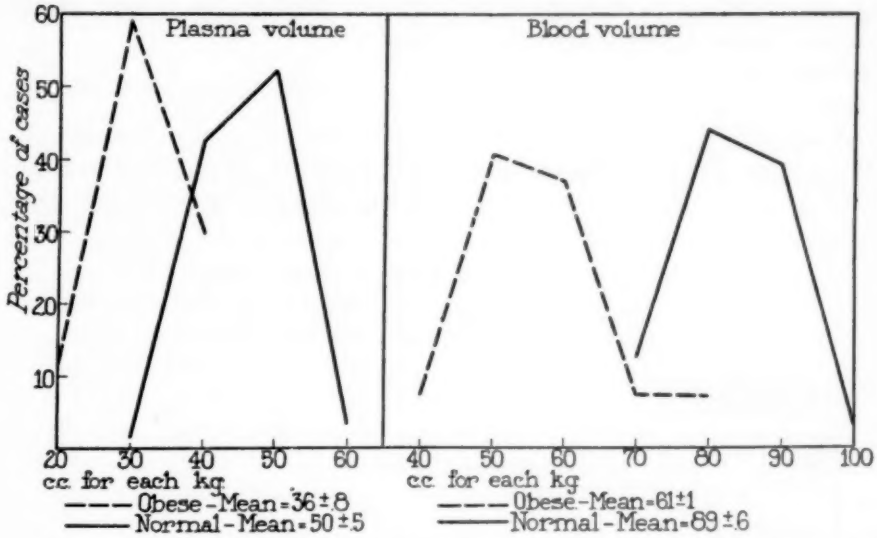

FIG. 2. Percentage distribution of relative blood and plasma volume in normal and obese subjects on the basis of body weight.

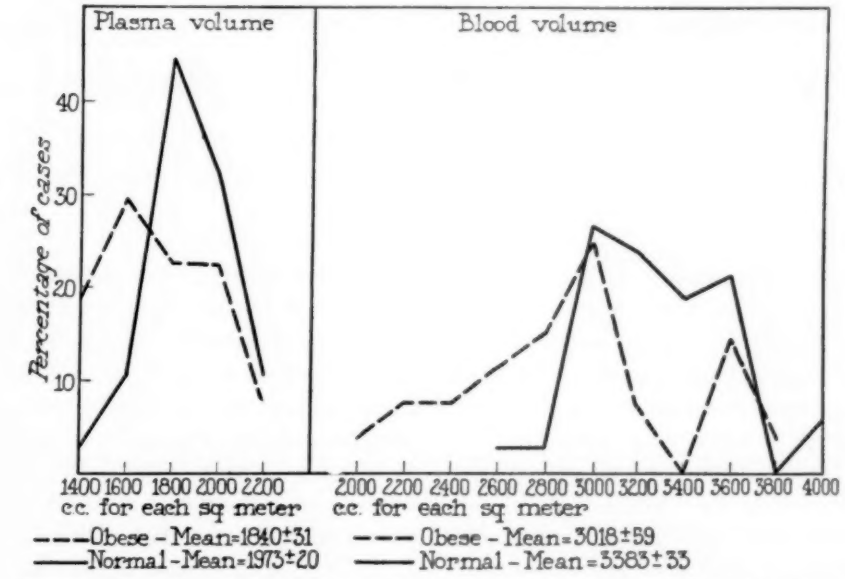

FIG. 3. Percentage distribution of relative blood and plasma volume in normal and obese subjects on the basis of surface area.

a condition of "simple hypervolemia." This is probably a compensatory reaction to secure a larger amount of circulating blood. In the edema of diabetic patients on alkaline treatment the blood picture was normal.

We may encounter degrees of edema in the presence of decreased blood volume and normal plasma volume (glomerular nephritis), increased blood volume and increased plasma volume (nephrosis dilution?), increased blood volume with normal cell and plasma volumes (cardiac congestion), or normal blood volume and normal plasma volume (diabetic edema).

Obviously the blood can present only one of several pictures concerned. Its rôle would seem to be passive rather than active in the production of edema. It seems more than likely that the blood volume changes simply reflect changed relationships in the fluid balance between the tissues and kidneys.

Diseases of the blood

The diseases of the blood offer definite contrasts (Fig. 4). The smallest volume is found in pernicious anemia.

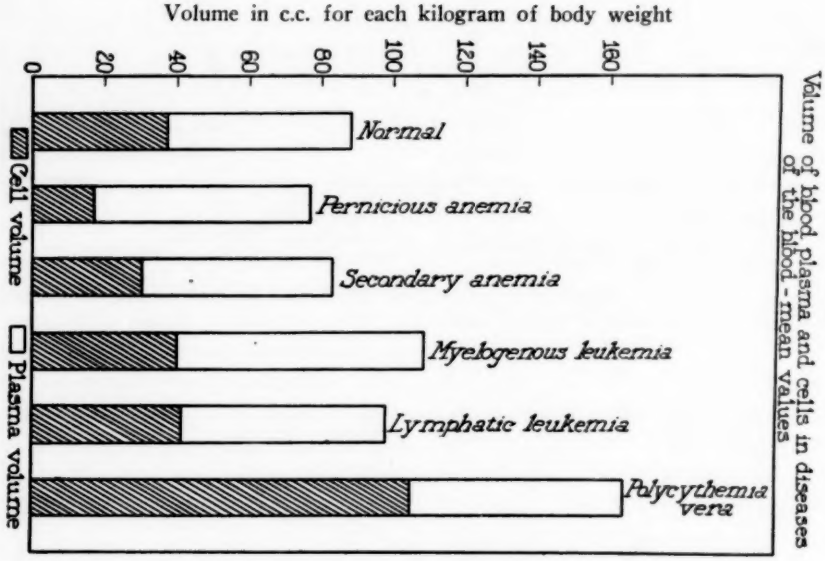

Fig. 4. Volume of blood plasma and cells in diseases of the blood, mean values on the basis of body weight.

In this the decrease in cell volume is striking but the loss is partly compensated by an increase in plasma volume. Decreased volume is also found in secondary anemia with plasma replacement about the same as obtains in primary anemia. Blood volume increases in both splenic and lymphatic forms of leukemia, high values being found for both plasma and cells. In polycythemia vera, on the other hand, there is a tremendous increase in red cells and blood volume with only a slight increase in plasma volume,

which, in itself, indicates the clinical need of studies of blood and plasma volume.

Comment

The increase in plasma, although striking in many diseases, has never entered into clinical conceptions of disease. Large plasma volume is noted in splenomegaly, splenic anemia, cirrhosis of the liver, hemolytic jaundice and leukemia, and a very low value in myxedema. Obviously more should be known fundamentally and clinically about plasma. Is plasma merely a vehicle for red cells? Is it not as important, if not more important, than erythrocytes in the supplying of metabolites to tissues and cells and in the removal of waste products? Is it a fluid tissue? Is it of itself subject to disease aside from disease involving the red and white blood cells or is it a mere passive fluid used in transportation? These and many other aspects of the plasma problem await investigation.

Finally we may group certain diseases according to whether they are characterized by increase or decrease in blood volume. In Table 1 are shown examples of diseases with a low volume of blood according to body weight. In Table 2 are listed the diseases in which there is an increased volume of blood for body weight. Finally Figure 5 indicates the values of blood volume, plasma volume and

Table 1

Small blood volume states*

Status	Cases	Blood volume, c.c.	Plasma volume, c.c.	Cell volume hematocrit	Comment
Normal	62	89	50	42	Simple normovolemia
Obesity	27	61	36	40	Simple hypovolemia
Myxedema	10	70	48	34	Oligocythemic hypovolemia
Anemia					
Secondary	17	82	52	31	Oligocythemic hypovolemia
Primary	9	77	60	23	Oligocythemic hypovolemia; Plasma replacement
Edema					
Glomerular nephritis	12	75	52	30	Oligocythemic hypovolemia
Surgical shock	30	66 60		30	Oligocythemic hypovolemia critical level (Keith)
Dehydration dogs	10	70	35	45	Polycythemic hypovolemia (Keith)

*According to body weight: Average values

Table 2

LARGE BLOOD VOLUME STATES*

Status	Cases	Blood volume, c.c.	Plasma volume, c.c.	Cell volume hematocrit	Comment
Normal	62	89	50	42	Simple normovolemia
Cirrhosis of liver	9	98	66	34	Oligocythemic hypervolemia
Banti's disease	16	98	68	30	Oligocythemic hypervolemia
Nephrosis	9	95	60	38	Oligocythemic hypervolemia
Diabetes insipidus	1	103 111	56 54	34 34	Five liters of water a day Oligocythemic hypervolemia Twenty liters of water a day
Water intoxication; dogs	30	104	64	37	Oligocythemic hypervolemia
Pregnancy	11	96	58	42	Simple hypervolemia
New-born infant	45	147	54	50	Polycythemic hypervolemia resulting in hemolytic jaundice
Polycythemia vera; after treatment with phenyl hydrazine	39 5	164 90	59 60	62	Polycythemic hypervolemia Oligocythemic normovolemia

*According to body weight: Average values

hemoglobin in polycythemia vera and the changes incident to treatment by phenylhydrazine. The decrease in the blood volume, number of erythrocytes, and percentage grams of hemoglobin are fairly parallel.

SUMMARY AND CONCLUSIONS

It is our opinion, based on a careful and protracted study of blood volume in disease states that the changes in volume of blood and plasma are just as definite and significant as changes in concentration. The latter are determined only as a routine, that is, the determination of hemoglobin and the count of red cells. The former, the volume of blood and plasma has been entirely neglected in medical practice.

The dye method of estimating blood volume as originally introduced is sufficiently accurate for clinical purposes and is entirely free from danger. We believe that changes in blood and plasma volume are of sufficient clinical value to warrant the adoption of this

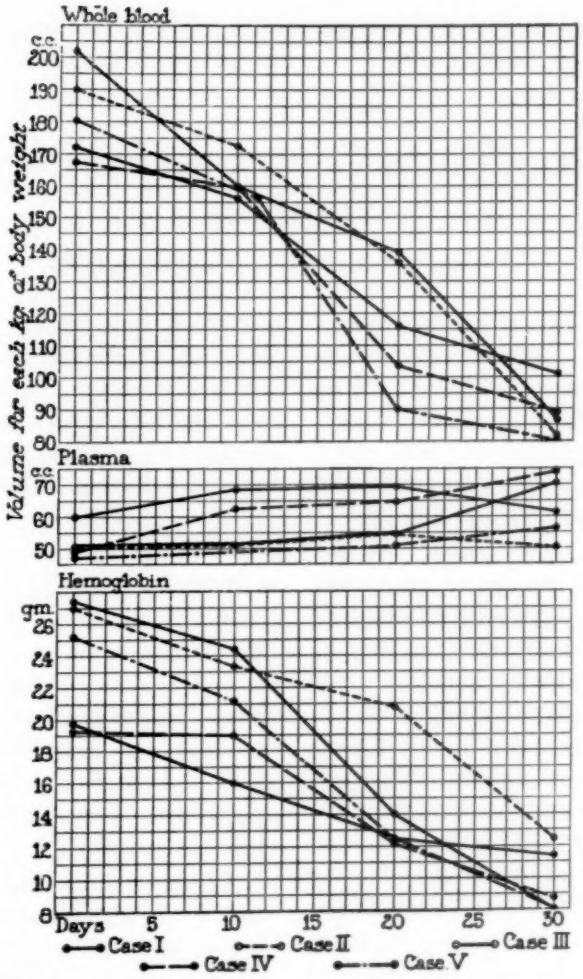

FIG. 5. Polycythemia vera. Reduction of blood and plasma volume and hemoglobin during treatment with phenylhydrazine hydrochloride.

study in clinical medicine. The true nature and significance of blood changes in disease cannot be fully appreciated or explained until a more complete study of the blood is undertaken clinically. The dye method offers an excellent approach to this investigation.

Cardiac Conditions Contra-indicating the Use of Digitalis*

By Joseph Sailer, M.D., *Philadelphia, Pa.*

In the reading of medical literature and in the practice of medicine, particularly if, as a result of hospital and consultation work, one is thrown much in contact with other physicians, one is impressed with the belief that exists in the efficacy of digitalis in all forms of heart disease. Heart-disease is by no means a uniform condition. Although the symptomatology does not vary so greatly, the conditions underlying these combinations of symptoms represent pathological conditions that differ fundamentally. It has seemed, therefore, worth while to make some attempt to discover whether there is any real basis for the profound faith in the efficacy of digitalis, or whether we should attempt more or less completely to differentiate the different forms of cardiac disorders, and to attempt to discover at the present day some appropriate treatment. From the standpoint of therapeutics, it is difficult to classify heart-disease; but as it is necessary to have a working basis, I am going to attempt some rough grouping which is as follows:

First, defects in conduction. These include all forms of heart-block, bundle block, arborization block, fibrillation, flutter, and probably there should be included among these the different varieties of auricular and ventricular premature contractions; because, indeed, the rhythmical conducting system is disturbed. Somewhat akin to these are disturbances in rhythm, particularly the paroxysmal tachycardias and nodal rhythm. Also akin to these are those disturbances which are due to conditions outside the heart, such as hyperthyroidism, infections, effort syndrome, and cerebral disturbances.

Then, and by no means entirely separate from some of the preceding conditions, we have inflammatory disturbances of the heart. These include acute endocarditis, acute pericarditis, and acute myocarditis,—the latter rather a curiosity.

Chronic valvular disease, and I have been much impressed, as have many others, with the desirability of differentiating the effects of the different valvular lesions, at least from the standpoint of treatment; chronic obliterative pericarditis; the heart of old age, or, as Cohn prefers to call it, the heart of senescence.

Finally, there is a large group of congenital forms of heart-disease, concerning which we know comparatively little, and for the treatment of which we have still less knowledge.

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*Read before the American College of Physicians, March 5, 1928, New Orleans, La.

The object of this paper is not to give definite statements regarding the the desirability of particular forms of treatment, with reference to their advantage or disadvantage. The chief object is to propound questions to which I have not hitherto been able to secure satisfactory answers.

Cushny has been much impressed by the lack of intelligence in the use of digitalis. He states that disease of the heart was treated with digitalis almost without any attempt being made to notice whether it was equally efficient in all the conditions included under this heading, and without any satisfactory observation of the effect on the pulse. He believes that there was no progress in the use of digitalis during the entire 19th century. One of the reasons for this has been the inadequacy of our knowledge of the physiological action of the drug. To quote Cushny again, it is still undetermined whether it acts as a stimulant or a sedative, and without a clear knowledge of this point, its use must still remain empirical.

What is actually known of the action of digitalis is curiously little, when one contemplates the enormous number of experiments that have been made and the vast amounts of literature that has resulted from them, not to consider the various therapeutic expositions and the attempts made to learn something definite by clinical observation.

We know that digitalis slows the heart's action, and that it does this by acting upon a brain center, presumably in the medulla; that the result of this action is transmitted along the vagus nerves to the heart. This slowing consists in a lengthening of the A-V interval, and a prolongation of the diastolic interval. We know, further, that each contraction of the heart under the medical action of digitalis is strong, but that the total work of the heart is not necessarily incraesed, because there are fewer contractions per minute.

The effect of lethal doses need hardly be considered. The auricular contractions are variable; the ventricle may intermit, and the auricle may cease to beat. Perfusion of the excised heart with Ringer's solution to which digitalis has been added gives rise to variable results. The slow pulse may be relieved by the application of atropin. An interesting experiment has been performed by severing the turtle's heart from its body, the only connection remaining being through the vagus nerves. If then the turtle's head is perfused with digitalis, the pulse is slowed in the usual way, showing that local action is not essential.

With massive doses, heart-block occurs. It may occur in human beings to whom excessive clinical doses have been administered, as well as in animals, the first manifestation being the prolongation of the P-R interval, and then the complete dissociation between the auricular and ventricular beats. The toxic stage causes a great increase in the number of spontaneous beats produced by pacemakers in various parts of the heart. Digitalis may cause both auricular and ventricular fibrillation, the latter, of course, usually fatal.

In the laboratory it is very easy to demonstrate an increase in the blood-pressure after the administration of digitalis. It is much more difficult to

show that this is accomplished by therapeutic doses, and, indeed, it is questionable if therapeutic doses can increase the pressure in so-called essential hypertension. Other undesirable actions of digitalis are vomiting, colic and diarrhea,—possibly all of them central; and it is even at this late date undertermined exactly what is its effect upon the kidneys.

Nevertheless, there will be no disagreement, I think, that digitalis is of the utmost value in many forms of heart disease, even although the method by which it produces improvement is not known. In discussing the effect of digitalis upon defects in conduction, I shall take it for granted that the administration of digitalis in digitalis heart-block is necessarily bad. There is some question, however, regarding its effect upon heart-block due to other causes. Apparently a distinction must be made between incomplete heart-block and complete heart-block. Cushny, Sollmann and all others agree that in incomplete heart-block digitalis can only do harm, inasmuch as it will change the $\frac{II}{I}$ - $\frac{III}{I}$ type of heart-block to a complete form. In discussing the matter with clinicians, I have been impressed, however, with the fact that sometimes digitalis can do no harm in these cases, because the dose employed has been so small that no physiological action could be expected. Doses not exceeding 10 drops, of a possibly poor commercial tincture three times a day, are not likely to increase a partial heart-block. This is not a matter of scientific importance. It is not even a matter of rational therapeutics but it sometimes requires diplomacy to attempt to controvert the insistence of the physician that the digitalis has apparently been of benefit, even although he has used at the same time many other measures, particularly rest. Sollmann, however, is of the opinion that digitalis may be of some benefit in complete heart-block, inasmuch as it may stimulate the idio-ventricular contractions, and in that manner increase the activity of the heart and improve the circulation. Willius, however, does not believe that digitalis is helpful in these cases, even although the auricle may be fibrillating. My own experience has not been extensive, particularly because I have always felt that digitalis was necessarily contraindicated even in complete heart-block, and that other remedies offered a better chance of producing the results that Sollmann thinks might be produced by digitalis. Recently, however, there was a case of complete heart-block in my ward at the Philadelphia General Hospital, to which my Resident administered some digitalis. I was not averse to watching its effect. The heart's action was not increased, but the regularity of the ventricular contractions seemed to be better. As this patient, who belonged to the lowest class of society, had a bed in which he could rest for twenty-four hours, was given a suitable diet of well-prepared food, and felt, probably for the first time in years, assured of his bed and board, and therefore relieved of anxiety, it is quite possible that these other factors helped as much as, or even more than the digitalis in producing the effect. As the dose was very small, 1 c.c. of an assayed tincture three times a day, it can hardly be said that it proved the harmlessness of large doses of digitalis in complete

heart-block. Bachman has reported two cases in which strophanthus was used with doubtful benefit.

Branch bundle block is a condition for which we have practically only the electrocardiograph as a means of diagnosis. It is by no means uncommon. It is generally regarded as a serious lesion, but is compatible with many years of reasonably comfortable life; and there are some atypical forms which seem to interfere not at all with cardiac efficiency. I have one patient whose electrocardiogram for over twelve years has indicated this condition. The sole disability has been an occasional attack of tachycardia. He was on the front with the A. E. F. during the late war, and is able at the present time to play thirty-six holes of golf daily for a week at a time without discomfort. The existence of such cases renders it difficult to draw definite conclusions regarding the effect or non-effect of treatment. I have found little in the literature upon the treatment of this condition. The diagnosis has apparently been the most interesting feature. On theoretical grounds, anything which would further interfere with the conduction through the heart when one branch of the bundle of His has already been seriously damaged and perhaps completely incapacitated, should be carefully avoided. Nowhere have I found a statement of any clinician that he has recommended digitalis in this condition. I have never personally used it, and therefore I cannot say definitely that it does harm. That the heart may continue to act favorably for a considerable period of time, although the severe type of branch bundle block is present, and digitalis is not given, is a matter of general knowledge; and I shall present a lantern slide of such a case, who died of an acute infection of the lungs four years after the branch bundle block was discovered, and presumably a longer period after it had developed.

The question of arborization block is considerably more difficult. In this, usually as a result of disturbances in the coronary circulation, certain groups of the conducting fibres are thrown out of activity, and there are two factors to be considered. First, the immediate effect of the embolus in the heart. This may be rapidly fatal, or the heart may recover. The recovery may be temporary, or reasonably complete, and it is to be supposed that sometimes there is the establishment of a collateral circulation which leaves the heart in almost as good condition as it was before, with only a scar on the ventricular muscle to betray the lesion which previously existed. If it could ever be definitely proved that digitalis stimulates the heart-muscle, improves its contractility and the force of the contractions, it might well be argued that the administration of digitalis in these conditions would be a distinct advantage. However, if its effect of diminishing the contractability of the bundle of His can be shown to extend to the other conducting fibres of the heart, then digitalis might be injurious. If some sequel occurs, such as fibrillation of the ventricle, as in the case recently reported by Levine, in which the administration of enormous doses of quinidin sulphate apparently saved the patient's life, necessarily there would be some question regarding the possible utility of digitalis; but in the case which has

been mentioned, Levine decided not to employ it. Clerc and Levy report the case of a woman with myocardial insufficiency who showed slight amelioration on digitalis, then developed cyanosis, tachycardia and erythemia and died in 4 days. There were found a mitral lesion and an infarct of the right auricle. Keith gave digitalis in one of these cases of incomplete bundle block with apparent benefit.

My own experience is somewhat scanty; but some of it, at least, very definite. I was asked to see a physician who had fallen upon the golf-links, suffering intense precordial pain. He was carried to the club-house, laid upon a sofa in the hall downstairs, and remained on that sofa until his death seven days later. His mind was perfectly clear. The pain was relieved by hypodermics of morphine. When I saw him on the third day, it seemed not impossible that recovery would occur. On the sixth day, his physician, feeling that he was not improving as he liked, and possibly at the request of the patient, administered some digitalis. He reported to me on the seventh day that the patient was greatly improved by this, but in less than twenty-four hours after the first dose of digitalis the patient died. No conclusion can be drawn from this. He might easily have died, whether the digitalis had been given or not; and whether as a result of his faith in the drug, or because it really gave him cardiac relief, it is quite possible that the digitalis did not contribute in any way to the fatal end.

However, I had another case in which an old woman was brought into the ward of the Presbyterian Hospital, suffering from the usual indications of coronary thrombosis, with the characteristic changes in the electrocardiogram. For three months she remained there, apparently improving, and the object of our solicitous care, for I was very anxious to observe how long it would be possible to keep her alive. At the end of this time the service changed, and my colleague immediately commenced digitalis therapy. Her death occurred in less than forty-eight hours after it was administered, although the dose was by no means large, 20 minims three times a day, probably, as nearly as I could determine, measured by a dropper. At the autopsy the coronary circulation was filled with mercury, and an x-ray taken of the heart. This showed complete block in the anterior coronary artery. Again the results are not absolutely conclusive, for anyone with an obliterated coronary artery, even although there is apparently a fairly well established collateral circulation, must be expected to die at any time; and the digitalis may have had nothing to do with the result. But at least it can be assumed in both cases, that the digitalis did not serve in any way to prevent the fatal result. Pardee reports a case of coronary thrombosis that recovered. Digitalis was not given, so that its use is not essential to recovery.

I shall not discuss either auricular fibrillation or flutter. Both forms of block have so incontestably benefited by the administration of digitalis that they do not properly belong to this essay. Even in the fibrillation that may accompany abdominal septic infection is benfited by digitalis or quinidin according to Felberbaum and Finesilver.

Paroxysmal tachycardia is a name

used to designate several varieties of cardiac disturbances. In all of these varieties digitalis has been used. In all of them it has failed to slow the action of the heart. Whether there is some substance in the circulation which acts, as atropin does, upon the center in the medulla, and prevents its receiving the digitalis stimulation, or whether there is some other factor whose nature we cannot even surmise, in these cases digitalis can do distinct harm if pushed until it produces toxic effects. Then it is even possible that it has an injurious effect upon the brain. It is hardly worth while to continue the discussion of this form of heart-disease, because it is so generally admitted that digitalis is futile.

The same is true of nodal rhythm, in which apparently the pace-maker is dislocated to the node of Tawara, or somewhere in its neighborhood. Digitalis seems to have no effect in these cases. It does not appreciably stimulate the force of the contraction, for there is no reason to suppose that this is insufficient, nor has it any tendency whatever to restore the normal rhythm; at least I have come across no references to this. Jones and White report two cases of atrioventricular nodal rhythm in which digitalis was not given. One of the cases proved to be coronary thrombosis. It is also reasonable to suppose that coupled beats and pulsus bigeminus, as are produced by over doses of digitalis, can hardly be relieved by this drug. Conner describes an unusual type of gallop rhythm, that might occur during digitalis treatment but was not apparently caused by it.

There is more difficulty, however, in determining the value of digitalis in the tachycardias that occur in soldier's heart, or effort syndrome, in exophthalmic goitre, in infectious diseases, and in the tachycardias of functional cerebral disturbances. The latter, I believe, are so closely akin to effort syndrome, that they may be considered together. As long ago as the Civil War, Dr. da Costa of Philadelphia found that digitalis was of no value in these conditions. The experience in the late war only confirmed and emphasized this view. Even large doses of digitalis had no effect upon the rate of the pulse, and seemed to have a very bad effect upon the patient, so that they became more nervous and distressed than they were before its administration.

Hyperthyroidism is sometimes complicated by auricular fibrillation. The majority of those who have studied this complication, such as Foster, Anderson, and others are of the opinion that digitalis is beneficial. Plummer who has had such a large experience in these cases, in a paper read before the Association of American Physicians, believed that digitalis might be injurious. At the time that paper was read, not a single physician who discussed it differed from his opinion. Nevertheless, those who believe in the use of digitalis in cases of hyperthyroidism, complicated by auricular fibrillation, have continued to report excellent results. If I may express a personal opinion, it is that the auricular fibrillation of hyperthyroidism is not as obstinate as the auricular fibrillation that occurs in mitral disease, especially mitral stenosis; that it responds fairly readily to digitalis therapy, and that after it has been relieved, the patient seems better than before. It has

not yet, at any rate, been definitely proved that digitalis, if properly employed, is injurious in selected cases of toxic goitre.

I am very loath to discuss at all the question of the use of digitalis in infectious diseases. There is no doubt that at the present day it is almost univerally employed in these conditions. I do not think that I have been called to see a case of pneumonia for a long time that had not been receiving digitalis before I saw the patient. The use of digitalis in pneumonia antedates by many years the late war. Cohn gave a reason for its use, and urged it very strongly There is no question at all that digitalis in infectious disease with tachycardia fails to slow the heart, even in large doses. The reason that Cohn gave for its use was that in pneumonia, particularly, auricular fibrillation was not uncommon; and that when it occurred, if the patient were partially digitalized, it was easy to complete the digitalization, and in this way the chance of recovery was enhanced. Stuart Hart was opposed to this view. Cushny is of the opinion that if auricular fibrillation occurs, it is time enough to digitalize the patient when it is discovered. On the other hand, it may be that partial digitalization prevents its occurrence, and that when it does appear, it is such a serious complication that there is rarely time to wait until complete digitalization is accomplished.

In an experience at Camp Wheeler, where I was stationed during the first period of my service, we had 1500 cases of croupous pneumonia. These were studied as well as possible, typed, and in many cases blood-cultures were obtained. They were all in young men, nearly all of them in good condition, although some of the patients had recently had measles, and others had recently had attacks of the mild, early epidemic of influenza. No cases of irregularity of the pulse was noted. We had neither polygraph nor electrocardiograph, and therefore it is possible that cases were overlooked; but I do not think that I have ever worked with a more enthusiastic group of men than were the ward surgeons on the Medical Service at Camp Wheeler, and I believe that if cases were missed, at any rate our mortality was satisfactory. Very few of these patients received digitalis.

In my hospital services, where I receive many cases of pneumonia every year, where we have the advantage of using the electrocardiograph, auricular fibrillation is rarely detected, and digitalis in view of this is rarely given. It must be admitted that the administration of digitalis during the course of pneumonia, typhoid fever, or other infectious disease, has never been shown to be injurious. Some experimental evidence that digitalis may be of value in the circulatory disturbance produced by diphtheria toxin is offered by Gold. I may mention that Wyckoff and Boldring proclaim ovabain is not of much use in febrile conditions. They regard clinical improvement as the only criterion.

There is no evidence at the present time that digitalis is of any value in acute endocarditis, myocarditis, or pericarditis. Morrison in a study of 145 cases of subacute bacterial endocarditis in the records of the Massachusetts General Hospital reaches the conclusion that all treatment is futile. Neither is there any evidence that it

does much harm, although in one case that I shall mention later the distress following an attempt to digitalize the patient was rather startling. Moderate doses of digitalis in endocarditis, as in all other conditions, are practically harmless, and probably not very effective. We know too little about acute myocarditis, and it usually kills so rapidly, that the question of therapeutics rarely arises. I have had within the last five years two cases of abscess of the myocardium, neither of them suspected during life; one was a complication of a diabetic carbuncle; the other was a complication of liver abscess; and in neither patient was the serious condition of the heart recognized. Joachim and Mays report a case of calcified cardiac aneurism, in which massive doses of digitalis relieved an attack of cardiac weakness and tachycardia, but failed, as did quinidin, to relieve a second attack and the patient died.

The value of digitalis in valvular disease has been a question of much dispute. There seems to be no essential disagreement among clinicians that in disease of the mitral valve, digitalis will often serve to restore compensation; when compensation is restored, digitalis aids to maintain it, and there is no evidence that, used properly, it ever does any harm. This is particularly true of mitral stenosis; and various theoretical explanations have been advanced to explain why it does so. Theoretical explanations for physical signs, or the effect of treatment in heart-disease, have usually been wrong, and therefore should be entirely avoided.

The argument was waged about the effect of digitalis in aortic insufficiency. It is permissible to mention in this condition the explanation that digitalis, by prolonging the diastole of the heart, permitted more blood to flow back into it through the incompetent aortic valves, and actually increased the seriousness of the condition, for theoretically, it is desirable to make the diastolic pause as brief as possible, in order that more blood should remain in the general circulation. One might easily argue on the other side that the increased velocity of blood through the general circulation compensated for the small amount that could flow back into the ventricle; I mean the small amount that is compatible with cardiac compensation; for when severe decompensation occurs in aortic insufficiency, it is usually impossible to restore the heart to a compensated condition. Christian, however, and others have criticized this statement. Christian particularly finds that digitalis is quite useful in aortic insufficiency. It seems to steady the heart, to relieve the patient, and perhaps to promote diuresis, and is therefore a valuable drug. It must be remembered that mitral stenosis may be mistaken for aortic insufficiency and that digitalis naturally relieves it. Holt has reported such a case.

It will be generally admitted, I think, that in aortic regurgitation, the antisyphilitic remedies have been of some, but very doubtful benefit; and that the most important remedial measure that we have is rest, perhaps accompanied by some forms of physical therapy. On one occasion I saw a boy of 15 years, who had a rheumatic aortic insufficiency. This had apparently occurred when he was 8 years of age. His compensation had been good, and he had

played on various athletic teams in his school, being particularly noted for his strength and quickness. He had a mild attack of decompensation following the football season; and I placed him in bed, and he made a fairly good recovery, returning to school. Within a month, however, he developed signs of acute endocarditis, which was supposed to be due to the streptococcus cardio-arthritidis. During this attack the heart became steadily worse. He was treated with vaccine, which apparently had a moderately bad effect. During my absence from the city, one of my colleagues who saw him decided he was doing badly, and thought it would be worth while to attempt to digitalize him. He was therefore given in one day 8 c.c. of an assayed tincture of digitalis. He became so much worse immediately, that it was almost impossible not to regard the digitalis as having been injurious. In three days he died. He would surely have died if the digitalis had not been given. The only question that arises in our minds is, whether it might have hastened his death. It was considered that he may have had in addition to his acute endocarditis some myocarditis, and we also considered the question as to whether the results of the aortic insufficiency were made more severe by the administration of digitalis or not.

I do not know anything, nor have I been able to find anything in literature, regarding any effective treatment for congenital heart-disease. The patients that I have had, and in which I felt that I could recognize this condition with any certainty, were treated entirely by rest, although as digitalis seems more useful when right preponderance is present than when left preponderance is present, and as all cases of congenital heart disease have right preponderance, it may easily be true that digitalis is helpful.

There are three other conditions which should properly be discussed. The first is chronic obliterative pericarditis. This depends upon the extent of the obliteration. If it is both endo- and exo-pericarditis, nothing is of much help. The heart apparently dilates, decompensation becomes severe, and the patient dies. Simple exo-pericarditis is difficult to recognize during life. It rarely gives rise to much enlargement of the heart or to much decompensation and probably never requires treatment. Endo-pericarditis may be compatible with a considerable duration of life. I had one patient with a very distinct Broadbent sign in my ward for three years, and used him for demonstration to innumerable ward-classes. His heart was very large; but the lazy life he led as a ward patient seemed to agree with him excellently; and until shortly before his death he was practically compensated. In these cases digitalis is often recommended, but there is great question as to whether it ever does any actual good. Perhaps in slowing the heart's action it diminishes the frequency of the tugs of the heart-muscle against the parietal pericardium, and may save the heart exertion. This is another of those theoretical explanations.

The heart in old age has been very much discussed. The comfort that is often experienced by physicians in administering small doses of digitalis in these old people is so great, that in the absence of any distinct evidence

of injury from the digitalis, there is no reason why it should not be given. It is very difficult, however, to prove that it does any good. Sollmann thinks that if the cardiac muscle is degenerated digitalis will be useless or even harmful because it imposes too great a task upon the remaining weakened muscle fibres.

This does not apply, of course, to the cases of auricular fibrillation in old persons, which should be treated in the same way that auricular fibrillation should be treated in all other patients. Marvin advocates digitalis in the dropsies of congestive heart failure, returning to Withington's original contention.

The use of digitalis in hypertension has also been discussed. O'Hare believes that it is never contraindicated. Cushny and Sollmann lay emphasis upon the fact that digitalis in therapeutic doses never increases the blood-pressure. There is therefore no reason why it should not be used; but it remains to be shown that it does any particular good. Sollmann has shown that the intravenous administration of digitalis gives rise to a fall in the blood-pressure, but this is only temporary. However, it is no more temporary than the fall which is produced by the administration of nitroglycerin; but in what way the slowing of the heart, or the impairment in cardiac conduction can help a patient who is suffering from the so-called essential hypertension, is not clear, and therefore the burden of proof, I think, at the present time rests upon those who advocate digitalis in these conditions to show how it may be of benefit.

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Clinical and Pathological Evidence of the Influence of Iodine in the Therapy of Primary Hyperthyroidism*†

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After more than a century of familiarity with the isolation and identification of iodine (Coindet 1820) and a growing knowledge of its natural distribution in plant and animal life, its agency in the physiology of the latter, and man in particular, is as yet not thoroughly understood.

In the accounts of medical practices of the many centuries of the past, are records of the uses of iodine in many body ailments and especially in goiterous enlargements of the neck. Its use in the latter condition gradually became rationalized (1) by the determination of the presence of iodine as a natural constituent of the thyroid gland (Bowman 1895), (2) by the experiments of Marine and Lenhardt who protected animals (dogs and fish) from goiterous enlargements by the addition of the required amount of iodine to their food; (3) by the further experiments by these authors (Marine and Lenhardt), (1) on regeneration and hyperplasia in the thyroid as influenced by iodine; (4) by the isolation and identification of thyroxin as the active principle of the thyroid (Kendall, 1914) and (5) by the observations of Plummer and Boothby concerning its clinical use in instances of hyperactivity. To these might be added many other similar experiments and studies all of which tended to point out the specific role of iodine in the physiology of the thyroid both in health and disease.

While these important advances, relative to the identification of iodine, as a positive and necessary factor in thyroid function were being made, many clinical observations were also made with a view to a better understanding of the then empirical use of iodine in thyroid dysfunction. Iodine was used in its crude form (ashes of sponge or seaweed) for many thousands of years, as a remedial agent, in so-called goiter. The purification of iodine and its compounds led to more accurate dosage and the development of various means of administration. The results

(1) Marine, David and Lenhardt: Arch. Int. Med. 4:440 (Nov.) 1909.

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were not wholly satisfactory because of the lack of control of clinical conditions and the inability of early clinicians to accurately differentiate the different types of thyroid disease. But from the time of the establishment of Parry's disease (1786) as an entity it was considered as unwise to use iodine in the therapy of this condition. Occasionally, however, on account of erroneous diagnosis or by accident, iodine was administered and beneficial results were noted. Trousseau (2)

(2) Clinical Lectures 1:587, Trans. By Bazire, New Sydenham Soc., 1868.

(1863) by mistake, gave tincture of iodine instead of tincture of digitalis to a patient with a supposed primary cardiac irregularity, which was probably secondary to hyperthyroidism. Improvement of the patient was noted and recurrence of the symptoms was observed when the correction was made. Numerous other instances of the beneficial uses of iodine in so-called exophthalmic goiter were recorded, but in general the results were bad and in many of the large clinics of Europe the use of iodine in this disease fell into disrepute. But surgery, one of the oldest methods of treating goiters, was productive of a mortality rate so high in primary hyperthyroidism that frantic efforts were constantly being made to better its technic and search for further aids in the therapy of this condition. The introduction of bed rest, isolation of clinical types, the use of soporifics, and preliminary pole ligations helped to lower appreciably the mortality rate. In the meantime the effect of such partial surgical removal on the remaining gland stump was studied by Wagner (3), Horsley (4) and Halstead (5), who found that

(3) Wien Med. Bl., 7:771, 1884.
(4) Lancet, 2:1163, 1886.
(5) Johns Hopkins Hosp. Rep., 1:373, 1898.

reconstruction hyperplasia and hypertrophy occurred. This finding led to a further understanding of what surgery accomplished besides a mass removal of offending parenchyma. It also opened the way for a study of the additional effect of iodine as a therapeutic adjunct.

Following the introduction of this and other data, iodine began to be used in small doses as a prophylactic measure. About the same time Plummer, having in mind the possible toxicity of incompletely iodinized thyroxin and the variations in the symptomatology of the clinical types, suggested that the administration of Lugols' solution in instances of primary hyperthyroidism might be of value. Subsequently Plummer and Boothby (6) published the beneficial results of

(6) J. Iowa M. Soc., 14:66-73, 1924.

its use in selected cases. Similar reports by others began to appear. Starr and Segall (7) in a study of forty-

(7) Arch. Int. Med., 34:355-364 (Sept.) 1924.

two cases made additional observations. These authors determined that the detoxification rate (based upon per diem reduction in the basal metabolic rate) was 3.7 points, a rate similar to that obtained by Segall and Means (8)

(8) J. A. M. A., 69:33, 1917.

with sub-total thyroidectomy alone. They further pointed out, that in 48%

of these cases, iodine therapy had the same effect upon the basal metabolic rate as the removal of five-sixths of the gland; that iodine would not produce a permanency in the remission, recurrence being the rule; and that the return of intoxication would result in a much higher basal metabolic rate. They therefore concluded that no gap between iodine therapy and operation should be allowed. This conclusion was concurred in by Clute (9),

(9) J. A. M. A., 86:105-109, Jan. 9, 1926.

who regarded the "optimal time" for thyroidectomy to be within a period of two to three weeks after iodine therapy was started. During this time he observed the most marked clinical improvements and the greatest drop in the basal metabolic rate. He regarded operation within such a time limit as safe and also stressed the fact that the toxicity recurring after cessation of iodine treatment is greater than before its use, if surgical removal is not promptly instituted. He further concluded that in the severe cases iodine reduced the necessity of pole ligations from 51 to 13%, but that iodine even though administered over a long period of time does not cure exophthalmic goiter. Petren (10) regarded

(10) U gesk f. Laeger, 88:363-364, Apr., 1926. Abst. J. A. M. A., 87:77, July, 1926.

iodine as having a life saving action. He also noted that the symptoms reappeared after cessation of the treatment and recommended the use of roentgen rays and ligation as additional measures.

Marie (11) concluded that the results of the use of iodine in the treatment testifies only to the fact that a disproportion exists between the iodine content and the requirement of the organism at that time rather than a deficiency of iodine. Marine (12) later

(11) Presse Med., 34:58-583 (May, 1926). Abst. J. A. M. A., 81:66, July, 1926.

(12) Ann. Clin. Med., 5:942-949, Apr., 1927.

called attention to the injudicious use of iodine in too large amounts (Lugols' contains 125 mg. iodine per cc.) It was suggested by him that smaller amounts more nearly physiologic (1 mgm. daily) should be given. He spoke of "heroic doses" as a preoperative measure as dangerous, from which much harm has occurred and will continue to occur. Marine regarded the beneficial effects of iodine in Graves' disease as limited and its injurious effects as serious. He also stated that these injurious effects have increased during the last three years and are of more serious consequence, than those disturbances noted as a result of the use of various iodine containing substances as preventive measures. Marine explained the effect of iodine on the probable basis of colloid storage which holds back the secretion. He stated that when the secretion is released it is reestablished with full force and yields larger amounts, the gland becoming larger and more solid. Helwig's (13) views were in agree-

(13) Klin Wschnschrgt 5:2356-2357 (Dec.) 10, 1927.

ment with those of Marine. He concluded that iodine feeding called forth an enlargement of the follicles and a thickening of the colloid, and that in his experience the severest cases of

Basedow's disease were encountered after iodine administration.

Sager (14) in a recent study at the Mayo Clinic again called attention to the necessity of differentiating the types of the hyperthyroidism before the use of iodine, on the basis of Plummer's views referred to above. He quotes Plummer as regarding the action of iodine as due to one of three possibilities. (1) Complete iodinization of thyroxin in the tissues (possible but improbable). (2) Complete iodinization of thyroxin in the thyroid (most probable). (3) Blocking of the discharge of the hormone (also probable).

(14) Arch. Surg. 15:878-894, Dec. 7, 1927.

From these, and many other important studies of the past we learn that the efficiency of surgery and other forms of therapy have been augmented by the knowledge of the existence of an iodinized hormone. Further that pure iodine may be advantageously used as a valuable adjunct in the treatment of instances of hyperthyroidism. This latter accomplishment is relatively new, and is far from being completely understood in spite of the excellent contributions appearing in the literature.

We therefore consider it not amiss to record the analysis of the clinical and pathological evidences of the influence of iodine therapy in instances of primary hyperthyroidism in this endemic goiter area.

The data here analyzed are those gathered from instances of primary hyperthyroidism, comprising a series of consecutive instances in a group that constitutes about 12% of the total thyroid disturbances seen by us.

Great care was exercised in differentiating the primary forms from the types of so-called secondary hyperthyroidism. All of these patients were submitted to a combination of rest and iodine therapy, followed by operation. (Double thyroidectomy).

For the purposes of study the information concerning the 131 instances of primary hyperthyroidism was divided into three groups according to the age. Group 1, 15 to 25 years (average age 21 years); group 2, 26 to 50 years (average age 39); and group 3, above 50 years (average age 57 years). This division, while somewhat arbitrary nevertheless takes into consideration puberty and adolescence, procreation and the menopause, and the post climacteric periods in the respective groups.

The clinical data of these three groups were collected according to a plan, the object of which is to illustrate the effect of iodine administration on the subjective and objective clinical manifestations before and after its use and to correlate these phenomena with the pathological findings. Accordingly the facts were arranged under the headings of (1) Admittance data; (2) Pre-operative iodine therapy; (3) Operative; (4) Post-operative therapy; (5) Discharge record; (6) Pathological study (See charts 1 to 7 inclusive).

In a consideration of such clinical data one must keep in mind many factors that may influence the clinical syndrome ordinarily associated with hyperfunction of the thyroid. The usual characteristic symptoms such as fa-

CLINICAL AND PATHOLOGICAL EVIDENCE IN INSTANCES OF PRIMARY HYPERTHYROIDISM

INFLUENCED BY THE USE OF IODINE THERAPY

CHART I

Patients Ages Ranging From 0 to 25 Years Inclusive

ADMITTANCE HISTORY											IODINE AND REST THERAPY			PRE-OPERATIVE RECORD			OP.	POST-OPERATIVE I THERAPY			TIME OF DISCHARGE REC.				Acc. No.
Marital Condition			Age	Chief Clinical Symptoms	P	Blood Press. S	D	B.P.	BMR	Wt.	Lugol's Sol'n Amt.	Fre.	Dur.	T.	P.	R.	Wt. Spec. in Gms.	Form	Amt.	Fre.	T	P.	R	Dys Hos.	
F		S	20	Nerv.Wt. G.I.D.	114	144	80	64	55	133	3M	TID		98	113	27	50				99	94	20	9	17265
F	M		22	Exoph.Nerv.Wt.Ftg	124	140	80	60	75	123	5M	TID	1	98	92	20		Lug. Dr. Lugl	5M	BID	98	80	20	9	17728
F	M		24	Nerv.Rpd.Ht.Enl.	135	155	80	75	28	128	10M	TID	2	98	85	22	61	Lug. Dr.	10M	TID	99	90	20	6	14186
F	M		19	Resp.Dif.Enl. Nerv.4.Wt.Rpd.Ht.	100	130	90	40	28	115	5M	TID	2	97	100	20	71	Lug. Dr. Lugl	10M	TID	99	95	20	9	14818
F		S	22	Resp.Dif.Enl. Nerv.WtRpd.Ht.	100	124	60	64	25	114	10M	TID	6	98	95	22	62	Lug. Dr.			99	92	22	15	13624
F		S	18	Resp.Dif.2.Enl. Exoph.Nerv.Rpd.Ht	140	155	60	95	25	121	10M	TID	12	98	105	22	138	Lug. Dr. Lugl	4M	TID	98	95	18	19	13663
F		S	17	Enl. Exoph.Nerv.Rpd.Ht.	135	150	60	90	42	117	10M	TID	7	98	105	20	71	Lug. Dr. Lugl	10M	TID	99	95	20	14	13908
F	M		25	Rpd.Ht. Exoph.Nerv.4.Wt.	110	120	70	50	42	104	5M	TID	8	95	105	22	47	Lug. Dr. Lugl	5M	TID	99	95	20	13	15569
F	M		22	G.I.D. Wt.Nerv.Res.Dif.	100	130	60	70	32	116	5M	BID	5	98	98	22	18	Lug. Dr. Lugl	3M		98	85	20	9	17715
F		S	15	Dif. Nerv.Rpd.Ht.Resp.	120	130	70	60	10	116	5M	TID	13	99	140	25	105	Lug. Dr. Lugl	5M	TID	98	102	25	22	14211
F		S	23	Dif.Ftg.Enl. Nerv.4.Rpd.Ht.Res	130	150	75	75	38	139	10M	TID	5	98	100	25	115	Lug. Dr. Lugl	5M	TID	97	80	20	10	13648
F		S	24	Enl. Nerv.Rpd.Ht.Ftg.	90	130	80	50	40	110	5M	TID	3	98	82	22	27	Lug. Dr. Lugl	5M		98	80	20	12	17302
F		S	21	Dif.Enl. Nerv.4.WtRes.	120	160	80	80	35	138	10M	TID	2	98	90	20	35	Lug. Dr. Lugl	10M	TID	99	130	20	6	14047
M			22	Wkn.G.I.D. Exoph.Nerv.Wt	112				34	143	4M	TID	120	98	90	20	105	Lug. Dr. Lugl	10M	TID	97	72	20	7	14706
F		S	17	Nerv.Res.Dif.Enl.	110	120	60	60	40	130	5 M	TID	4	98	80	22					98	100	20	8	14661
F		S	25	Wkn. Rpd.Ht.Res.Dif.	130	122	74	48	40	90	5M	BID	3	95	94	21	22	Lug. Dr. Lugl	1M		98	88	20	6	16235
F	M		23	Dif.2.Ftg.Enl. Nerv.Rpd.Ht.Res.	140	148	74	74	42	119	10M	TID	10	99	130	18	136	Lug. Dr. Lugl	5M	BID	99	80	10	18	15055

KEY:-

CHIEF CLINICAL SYMPTOMS:- Exoph.- Exophthalmus, Nerv.- Nervousness, Wt.— Loss of Weight, Rpd. Ht.- Rapid Heart, Res. Dif. -Respiratory Difficulty, 1,2,or 3 -Degree of Res. Dif. , Ankles- Edema of Ankles, G.I.D.- Gastro-intestinal Disorders, Enl.- Enlarged Thyroid, Wkn.-Muscular Weakness.

CLINICAL AND PATHOLOGICAL EVIDENCE IN INSTANCE OF PRIMARY HYPERTHYROIDISM

INFLUENCED BY THE USE OF IODINE THERAPY

CHART II

Patient's Ages Ranging from 26 to 50 Years of Age.

ADMITTANCE HISTORY											IODINE AND REST THERAPY			PRE-OPERATIVE RECORD			OP.	POST-OPERATIVE I THERAPY			TIME OF DISCHARGE REC.				Acc. No.
Marital Sex		Age	Chief Clinical Sympt.	Blood Press. P	Syst	Dia	P.P.	BMR	Wt.	Lugol's Sol'n Amt.	Fre	Dur.	T	P	R	Wt. Spec in Gm.	Fm.	Amt	Fre	T	P	R	Dys How	
F	S	30	Nerv. H'dac. Resp.Dif.	100	125	75	50	35	89	5M	BID	6	98	101	20	10	Lug. Dr.	5M	Ex. 2 Ex.	97.	90	20	13	17344
M		34	Ftg. Enl. Nerv. Wt-.Rap.H. Resp. Dif.2	130	120	60	60	50	146	5M	BID	8	98	100	20	43	Lug. Dr.	5M		98	90	28	12	17365
F	M	39	Nerv. Wt-.Rap.Ht.Enl.	112	170	80	90	43	125	10M	BID	5	98	100	22	74	Lug. Dr.	8M	10x	99	100	22	11	17567
F	M	50	G.I.D. Nerv.4† Wt-. Rpd.Ht. Resp.Dif.	96	200	100	100	34	96	5M	BID	6	98	100	20	45				99	80	22	14	17650
F	M	39	Rap.Ht.Resp.Dif.2 Ftg.	100	120	70	50	35	107	8M	BID	3	98	80	25	19	Lug. Dr.	5M		98	100	25	7	17693
M		32	Ftg. Nerv. Wt- Rpd.Ht. Resp.Dif. 2	120	150	80	70	45	124	5M	TID	3	98	95	25	85	Lug. Dr.	5M	8x	98	90	24	7	18431
M		37	Exoph. Nerv. Wt-.	66	125	80	45	19	124	5M	BID	5	100	120		60	Lug.	5M	Dly.	97	70		16	16182
F	M	38	Ht. Resp.Dif.2 Exoph. Nerv. Wt.- Rpd.	110	125	80	45	30	135	5M	BID	3	98	100	20	11	Lug. Dr.			98	90	20	9	16239
M		37	Ftg. anl. Dis.Nerv. Exoph.Rpd.Ht. Resp.Dif.	108	108	68	40	18	126	5M	TID	4	101	135	20	53	Lug.	5M	TID	98	65	20	10	16310
F	M	30	Nerv. Hdac. Enlg.	120	180	90	90	45	129	10M	BID	5	98	100	20	6	Lug. Dr.	5M	Dly.	98	80	20	12	16433
M		27	Enl. Nerv. Wt.- Rpd.Ht. Resp.Dif. 2	120	165	80	85	34	136	5M	BID	4	98	100	20	107	Lug. Dr.	5M		98	72	18	8	16458
F	M	36	Nerv. Ftg. Rpd. Ht. Resp.Dif. 2	100	160	80	80	50	123	10M	BID	5	98	102	22	20				99	100	25	7	16479
F	M	40	Ftg. Enl. Wt.- Nerv.Rpd.Ht. Resp.Dif.	158	124	90	34	6	118	5M	TID	6	99	116	20	20				98	84	20	18	16536
F	M	26	Dif.2 Enl. Nerv.Wt.-Rpd.Ht. Res.	108	120	68	52	12	130	5M	BID	6	98	80	20	15	Lug. Drp.	5M	BID	99	75		14	16583
M		32	Nerv.Hdac.Ftg.	136	118	84	34	50	128	5M	BID	1	98	112	22	20	Lug. Drp.			99	100	20	7	16609
F	M	30	Ftg. Nerv.4 Hdac.Res.Dif.2	145	150	85	65	48	112	5M	TID	8	97	88	20	47	Lug. Drp.	5M		98	75	20	17	16664
F	M	48	Appetite ! Nerv.3.rpd.Ht.Res.Dif.	128	100	75	25	30	140	5M	TID	13	98	115	22	33	Lug. Drp.	5M		97	100	22	21	16695
F	M	32	Ftg. Enl. Nerv.wtvRpd.Ht.Res.Dif.	180	140	80	60	29	141	5M	BID	2	97	80	20	42	Lug. Drp.	5M		97	73	20	8	16804
F	M	40	Nerv.WtvRpd.Ht.Res.Dif.	120	112	78	34	38	116	5M	BID	4	98	108	25	18	Lug. Drp.	5M		98	92	22	10	16864
F	S	33	Exoph. Nerv.WtvRpd.Ht.Ftg.Enl.	116	176	90	86	42	119	10M	BID	8	98	95	20	47		5M	BID	99	98	20	4	16897

CLINICAL AND PATHOLOGICAL EVIDENCE IN INSTANCES OF PRIMARY HYPERTHYROIDISM

INFLUENCED BY THE USE OF IODINE THERAPY

CHART III

Patient's Ages Ranging From 25 to 50 Years of Age.

ADMITTANCE HISTORY												IODINE AND REST THERAPY				PRE-OPERATIVE RECORD			OP.	POST-OPERATIVE IODINE THERAPY			TIME OF DISCHARGE RECORD				Acc. No.
Marital				Chief Clinical Symptoms	Blood Press.				BMR	Wt.	Lugol's Sol'n				T	P	Res.	Wt. Spec. Gm.	Form	Amt.	Fre.	T	P	Res	Dys Hos	
Sex	Rel.	Civ.	Age		Pul.	Syst.	Dia.	P-P			Amt.	Fre.	Dur.														
F	M		42	Nerv.Hpd.Ht.Ens.Dif.A	120	150	90	60	36	145	5M	TID	4	98	85	30	45	Lugol	5M		98	85	20	8	16919
F	M		49	Dif.2.Ftg.Enl. Nerv.3.WtrHpd.Ht.Res.	100	120	60	60	42	94	5M	BID	2	98	80	20	40	Lug. Drip		BID	99	98	22	7	16940
F	M		38	Exoph.Nerv.WtrHpd.Ht.	90	140	100	40	35	151	5M	BID	6	98	125	25	20	Lug. Drip Lugol	5M	Dly.	99	112	24	11	15965
M			34	Dif.2.Ftg.Enl. Nerv.4.WtrHpd.Ht.Res.	100	150	80	70	50	141	5M	BID	3	98	100	20	140	Lug. Drip Lugol	5M	BID	97	73	20	17	15806
F	S		34	Dif.2.Exoph.Ftg.Enl Nerv.4.Wt.Hpd.Ht.Res.	110	145	80	65	40	127	5M	BID	1	96	95	25	34	Lug. Drip	5M	Dly	98	56	20	9	15690
F	M		25	Exoph.Nerv.WtrHpd.Ht.	110	120	70	50	42	104	5M	TID	8	99	105	22	47	Lug. Drp. Lugl	5M	Dly.	99	95	20	13	1556
M			47	Nerv.Hpd.Ht.Enl.	115	160	80	80	23	132	5M	Dly	10	97	95	22	43	Lug. Drp. Lugl	5M	Dly	99	85	20	9	15640
M			36	Nerv.Hpd.Ht.Enl.	125	140	80	80	38	125	5M 10M	BID TID	10	98	100	20	129	Lug. Drp. Lugl	5M	Dly	98		20	15	15687
F	M		38	Ht.Ft. Exoph.Nerv.Wt. Hpd.	125	170	80	90	40	126	5M	BID	2	99	90	20	58	Lug. Drp Lugol	5M	BID	99	90	20	6	15711
M			37	Enl. Exoph.2.Hpd.Ht.Hdac.	105	120			38	172	5M	BID	180				40								15554
F	M		33	Exoph.Enl.	100	140	80	60	42	140	10M	BID	4	99	144	20	50				99	80	22	9	17228
F	M		36	Nerv.WtrFtg.	100	132	74	58	56	112	5M	TID	4	99	144	20	51	Lug. Drp. Lugl	5M		99	80	22	12	17227
M			40	Resp.Dif.Ftg. Exoph.Nerv.4.Hpd.Ht.	104	132	68	64	50	150	5M	TID	4	98	90	25	62	Lug. Drp Lugl	5M		97	80	20	10	16262
F	M		47	Inor.Ap. Nerv.4.WtrHpt.Ht.	114	140	75	65	38	155	5M	BID	4	99	100	20	79	Lug. Drp. Lugl	5M		99	82	22	10	17257
F	M		29	Ht.Res.Dif.Enl. Exoph.Nerv.4.Wt.Hpd	118	130	68	62	49	140	5M	BID	5	98	115	20	75	Lug. Drp. Lugl	5M		96	95	25	15	17301
F.	M		38	Enl. Nerv.4.WtrHpd.Ht.Ftg	116	130	92	38	72	98	5M	TID	3	99	95	20	51	Lug. Drp. Lugl	12M		99	95	20		16829
F	M		41	Dif.2.Ftg. Nerv.WtrHpd.Ht.Res.D	102	128	70	58	55	133	5M	BID	4	98	80	20	51	Drp. Lug. Lugl	5M	BID	98	72	18	9	16803
F	M		39	Exoph.Nerv.4.WtrFtg.	128	146	80	66	73	136	5M	BID	3	98	90	23	39	Lugl	5M	Dly	98	75	20	8	16511
F	M		45	Res.Dif.Enl.Temp. Exoph.Nerv.4.Hpd.Ht.	120	180	100	80	60	107	5M	BID	1	98	130	28	30	Lugol	5M	BID	98	100	22	10	17297
F	M		38	Res.Dif.Enl. Exoph.Nerv.Wt.Hpt.Ht	110	150	80	70	62	119	5M	BID	6		150	20	170	Lug. Drp. Lugl	5M	Dly	97	80	20	15	17384

CLINICAL AND PATHOLOGICAL EVIDENCE IN INSTANCES OF PRIMARY HYPERTHYROIDISM

INFLUENCED BY THE USE OF IODINE THERAPY

CHART IV

Patients Ages Ranging From 26 to 50 Years Inclusive

ADMITTANCE HISTORY											IODINE AND REST THERAPY			PRE-OPERATIVE RECORD				CP.	POST-OPERATIVE I THER.			TIME OF DISCHARGE RECORDS				Acc. No.
Sex	Marital State	Age	Chief Clinical Symptoms	Pul	Blood Pressure Systo.	Dia.	P.P.	BMR	Wt.	Lugol's Sol'n Amt.	Pul.	Dur	T	Pul	Res	Wt. Spec. Gm.	Frm	Amt	Fre	T	Pul	R	Dys Hos	
F	M	46	Nerv.4.Wt7Res.Dif.	132	140	80	60	65	135	5M	BID	120	98	126	20	60	Lug. Drp. Lugl	5M	TID	97	76	22	11	17419
F	M	41	Nerv.4.Wt.Rpd.Ht.Enl	132	150	80	70	60	132	8M	TID	5	98	80	20	56	Lugl	8M	Dly	98	80	22	12	16604
F	M	38	Exoph.Nerv.Wt7Res.Dif.1	120	135	70	65	75	126	5M	TID	1	98	105	22	61	Lugl	5M		98	72	20	10	17449
F	M	39	Dif.GID. Exoph.Nerv.4.Rpd.Ht.Res.	132	135	70	65	75	147	5M	TID	5	97	105	22	79	Lug. Drp. Lugl	5M	TID	98	90	20	15	17534
F	M	35	Nerv.Rpd.Ht.Res.Dif.2.Ftg	126	150	84	66	75	125	5M	TID	15	99	100	22	90	Lug. Drp. Lugl	3M		98	72	20	21	17523
M		41	Nerv.4.Exoph.4.Enl.	126	130	70	60	66	185	10M	BID	4	97	95	20	108				97	80	22	10	17570
M		42	Enl. Exoph.Nerv.Res.Dif.Ftg.	132	164	140	24	86	148	10M	TID	5	97	125	22	123	Lug. Drp. Lugl	15M	5X Dly	98	120	20	13	17569
F	M	34	Enl.Rpd.Ht. Exoph.Nerv.Res.Dif.2.Ftg.	120	144	82	62	73	134	5M	BID	5	98	120	25	123	Lug. Drp. Lugl	5M	BID	99	85	20	11	17729
F	M	38	Ftg.Enl. Nerv.4.Wt.Rpd.Ht.Res.Dif.	94	140	90	50	51	118	6M	TID	1	96	72	20	36	Lug. Drp. Lugl	5M	BID	99	76	20	5	17735
F	M	45	Gld. Nerv.Wt.Rpd.Ht.Res.Dif.2	120	100	80	20	60	104	5M	BID	3	96	72	20	56	Lugl	5M	BID	97	86	20	9	17815
M		36	Nerv.Wt.Ftg.Nocturia Exop	96	140	70	70	54	111	10M	TID	1	98	75	22	64	Lugl	5M	QID	97	56	20	9	17816
M		48	Ftg. Exoph.Nerv.3.Wt7Res.Dif.1	106	134	78	56	65	100	8M	TID	8	99	106	25	40	Lugl Drp. Lugl	5M	TID	86	100	20	9	16199
F	M	38	Ftg.Enl.GID Nerv.Wt.Rpd.Ht.Res.Dif.2.	110	200	80	120	73	124	5M	TID	3	98	110	22	45	Lug. Drp.			98	80	20	8	16223
M		47	Exoph.Nerv.Wt.Rpd.Ht.Enl.	115	150	90	60	54	188	5M	BID	5	98	95	20	48	Lug. Drp.			99	90	20	9	14748
M		35	Nerv.4.Wt7Res.Dif.2.Ftg.	100	135	65	70	52	120	5M	TID	5	99	86	18	60	Lug. Drp.			99	80	20	12	14744
F	M	42	Exoph.Nerv.Wt.Rpd.Ht.Enl	125	140	80	60	54	107	10M	BID	4	98	120	22	12	Lug. Drp. Lugl	5M	TID	97	85	20	11	14745
M		38	Nerv.Wt.Rpd.Ht.Ftg.	120	151	100	51	99	118	10M	BID	7	98	112	20	65	Lug. Drp.			99	98	22	13	14782
F	M	39	Exoph.Nerv.4.Ftg.Enl.GID	130	136	76	60	88	102	10M	TID	13	98	85	22		Lug. Drp. Lugl	5M	TID	98	85	20	17	15283
M		39	Nerv.Wt.+10lb.Rpd.Ht.Enl.	120	150	90	60	80	-50	10M	TID	12	98	80	22	115	Lug. Drp. Lugl	5M	TID	99	90	20	17	15182
F	M	31	Dif.Enl. Exoph.Nerv.4.Rpd.Ht.Res.	130	190	90	90	68	103	6M	BID	6	99	92	20	70	Lug. Drp. Lugl	5M	BID	98	74	20	14	15799

CLINICAL AND PATHOLOGICAL EVIDENCE IN INSTANCES OF PRIMARY HYPERTHYROIDISM

INFLUENCED BY THE USE OF IODINE THERAPY

CHART V

Patients Ages Ranging From 26 to 50 Years Inclusive

ADMITTANCE HISTORY												IODINE AND REST THERAPY			PRE-OPERATIVE RECORD				OP.	POST-OPERATIVE THERAPY			TIME OF DISCHARGE			REC.	Acc. No.
Sex	Marital Status		Age	Chief Clinical Symptoms	Pul	Blood Press. Syst	Dia.	P.P.	BMR	Wt.		Lugol's Amt.	Sol. Pul	Dur	T	Pul	Res	Wt. Spec Gm.	Form	Amt	Fre.	T	Pul	R	Dys Norm	
M			40	Exoph.Nerv.4.Wtr2nd.Ht.Res.Dif	120	135	80	55	54	144		5M	TID	2	98	88	20	41	Lug. Drp.			98	72	20	22	14458
F	M		40	Exoph.Nerv.Wtr.Rpd.Ht.Enl.	135	180	100	80	50	124		5M	BID	4	98	85	22	43	Lug. Drp. Lugl	5M	Dly.	98	80	20	12	15314
F	S		26	Wtr.Res.Dif.1.Enl.	110	115	68	47	30	104		15M	Dly	16	98	100	20	38	Lug. Drp.			98	96	20	21	15312
F	M		47	Nerv.Rpd.Ht.Res.Dif.2	96	134	84	40	42			10M	TID	3	98	106	22	0				99	95	20	14	13850
F	S		32	Ftg.Enl. Nerv.Rpd.Ht.Res.Dif.2.GID.Wtr	120	120	80	40	40	121		10M	TID	9	98	90	20	57	Lugl	10M	TID	100	85	22	19	13699
M			38	Exoph.4.Nerv.4.Wtr	120	160	100	60	40	117		10M	TID	3	98	120	20	55	Lug. Drp.			98	80	25	8	13789
M			43	Nerv.3.WtrRpd.Ht.Res.Dif.2.Enl	110	165	90	75	28	127		10M	TID	2	98	100	20	47	Lugl	10M	TID	98	85	20	7	14512
F	S		38	Enl. Exoph.Nerv.3.Rpd.Ht.Res.Dif.	100	130	80	50	30	118		10M	TID	10	98	95	22	139	Lug. Drp. Lugl	10M	TID	98	88	22	10	13733
F	M		33	Nerv.WtrRes.Difl.Freq.Mictur.	85				20			10M	TID	4	98	75	20	25	Lug. Drp			98	75	25	9	13900
F	M		31	Dif.2.Enl.GID Exoph.Nerv.4.Rpd.Ht.Wtr.Res.	120	170	80	90	30	129		6M	TID	5	99	90	25					99	92	22	14	1298)
M			32	Nerv.Wtr.Rpd.Ht.	130	135	60	75	38	178		10M	T+D	2	99	100	22	17	Lug Drp Lugl	10M	TID	99	90	20	8	14437
F	M		29	Nerv.4.WtrRpd.Ht.Res.Dif.Enl.	110	110	90	20	45	144		10M	TID	7	98	85	20	112	Lugl	10M	TID	99	95	20	12	14316
M			40	Wtr.Sleepy.Cold hands.	80				8	186		10M	TID	1	97	73	20	62				98	75	20	5	14286
F	M		36	Nerv.Insom.Excess.Appe.	140	150	85	64	20	155		10M	TID	21	99	132	20		Lug Drp Lugl	5M	TID	98	95	20	150	14318
M			36	Rpd.Ht.Res.Dif.2.Ftg.	92	145	80	65	38	136		5M	TID	6	97	95	20	16				97	72	20	11	14094
F	M		47	Exoph.Nerv.Rpd.Ht.Enl.	130	165	70	95	40	122		10M	TID	5	98	98	20	54	Lug. Drp.			98	100	20		14089
F	M		40	Wtr.Rpd.Ht.Ftg.	150				32			10M	TID	5	98	115	22	42	Lugl	5M	TID	98	90	20	12	14888
F	M		46	Dif.Enl. Exoph.Nerv.3.WtrRpd.Ht.Res.	120	155	70	85	44	137		10M	TID	5	99	110	22	102	Lug. Drp. Lugl	10M	TID	98	100	20	13	14588
F	M		35	Dif.2.Enl. Exoph.Nerv.4.Wtr.Rpd.Ht.Res.	100	140	70	70	32	95		10M	TID	3	99	115	20	86	Lug. Drp. Lugl	10M	TID	98	75	20	10	14600
F	M		29	Wtr. Nerv.4.Rpd.Ht.Res.Dif.2.Enl.	100	135	70	65	34	134		10M	TID	5	99	125	22	40	Lug. Drp. Lugl	10M	TID	98	80	22	13	14932

CLINICAL AND PATHOLOGICAL EVIDENCE IN INSTANCES OF PRIMARY HYPERTHYROIDISM

INFLUENCED BY THE USE OF IODINE THERAPY

CHART VI

Patients Ages Ranging From 25 to 50 Years Inclusive

ADMITTANCE HISTORY												IODINE AND Post THERAPY			PRE-OPERATIVE RECORD				OP.	POST-OPERATIVE I THER.			TIME OF DIS-CHARGE RECORD				Acc. no.
Sex	Marital State		Age	Chief Clinical Symptoms	Pulse	Blood Press. Sys	Dia	P.P.	BMR	Wt.	Lugol's Sol'n Amt.	Ful	Dur.	T.	Pul.	Res.	Wt. Spec. Gm.	Prep	Amt	Pre	T	Pul	R	Dys Hos	
F	S		26	Ht.Enl. Nerv.4.WtrRes.Dif.2.Rpd.	120	130	75	55	50	98	10M	TID	2	98	105	22	50	Lug. Drp. Lugl	10M	TID	99	88	20	7	14991
F	M		40	GID.Enl. Nerv.4.Rpd.Ht.Res.Dif.2.	130	116	80	38	45	142	10M	TID	6	99	100	20	29	Lugl	5M	Dly	99	82	20	12	15070
F	M		36	Nerv.3.WtrRpd.Ht.Res.Dif.	125	130	80	50	31		5M	TID	3	99	125	20	35	Lugl	5M	TID	98	80	20	12	15065
F	M		30	Exoph.Nerv.4.WtrGID.4.Enl	118	120	78	42	45	108	10M	TID	2	97	95	20	42	Lug. Drp.		BID	98	100	20	7	15060
F	M		32	Hoarseness Exoph.Nerv.1.Rpd.Ht.Enl.	100	150	80	70	29	124	10M	TID	2	98	80	18	181	Lug. Drp.		Dly	98	82	20	12	15121
F	M		39	Nerv.WtrRpd.Ht.Enl.GID.	90	130	80	50	30	102	10M	TID	3	97	80	22	35	Lug. Drp.			97	72	20	13	15155
F	M		33	Nerv.4.WtrRes.Dif.2.	160	140	50	90	37		5M	BID	3	98	100	22	40	Lug. Drp.			98	106	20	8	16369
F	M		30	Nerv.Ftg.	136				32	133	5M	TID	8	99	100	20	48	Lug. Drp.			98	95	20	15	16770
F	M		35	Rpd.Ht.Enl.Ftg. Exoph.Nerv.3.WtrRes.Dif.2	120	130	90	40	27	124	5M	TID	10	98	126	20	61	Lug. Drp. Lugl	5M		99	80	20	16	16988
F	M		32	Nerv.WtrRpd.Ht.Enl.	120	130	80	50	40	95	5M	BID	3	98	115	25	74	Lugl	5M		97	78	20	9	417011
F	M		36	Nerv.1.Rpd.Ht.Ftg.Enl.GID	130	140	80	60	73	138	5M	TID	3	98	99	25	39	Drp. Lugl	5M	Dly	99	92	20	8	16269
F	M		28	Ftg.Enl.GID Exoph.Nerv.4.WtrRpd.Ht.	120	136	80	56	60	117	5M	TID	5	99	120	22	110				98	90	20	8	16288
F	S		30	Nerv.WtrRpd.Ht.Enl.	120	168	68	100	60	99	5M	BID	11	98	1115	20	69	Lug. Drp. Lugl	5M	BID	98	72	20	21	16291
F	M		46	Dif.Ftg.GID. Exoph.Nerv.WtrRpd.Ht.Res.	100	210	100	110	61	158	5M	TID	2	99	85	22	58	Lug. Drp.			99	80	22	9	16510
F	M		35	GID. Nerv.WtrRpd.Ht.Res.Dif.	110	140	80	60	60	116	5M	TID	5	98	90	22	41	Lugl	5M	Dly	97	72	20	11	16663
F	M		41	Rpd.Ht. Exoph.Nerv.4.WtrRes.Dif.	120	160	80	80	51	132	5M	BID	3	98	85	25	55	Lug. Drp. Lugl	5M	BID	98	75	20	11	16729
F	M		38	Nerv.4.WtrRpd.Ht.Ftg.Enl.	116	130	92	38	72	98	5M	TID	3	99	95	20	60	Lug. Drp. Lugl	12M	Dly	99	98	20	14	16829
F	M		34	Ftg.Enl. Exoph.1.Nerv.4.Res.Dif.	110	165	80	85	56	160	8M	TID	3	98	100	20	69	Lug. Drp. Lugl	5M	Dly	98	73	18	8	16891
M			33	Enl. Nerv.4.WtrRes.Dif.2.Ftg.	100	130	70	60	60	114	5M	TID	9	99	100	20	68	Lug. Drp. Lugl	5M	TID	98	100	20	16	16894
F	M		33	Nerv.WtrRpd.Ht.Res.Dif.	120	140	70	70	74	141	5M	BID	3	97	95	20	49	Lug. Drp. Lugl	5M	BID	97	72	20	8	17016

KEY:-

CHIEF CLINICAL SYMPTOMS:- Exoph.-Exophthalmos, Nerv.- Nervousness, Wt.-- Loss of Weight, Rpd.Ht.- Rapid Heart, Res.Dif.- Respiratory Difficulty, 1,2,or 3 - Degree of Res.Dif., Ankles.-Edema of Ankles, G.I.D.- Gastro-Intestinal Disorders, Enl.- Enlarged Thyroid, Wkn.- Muscular Weakness.

tigue, exhaustion, weakness, loss of weight, nervousness, rapid heart, respiratory difficulties were present in all of the cases and in a number (15) variation in appetite, nausea, vomiting and diarrhea.

Exophthalmos was observed five times in each of groups 1 and 3 and 36 times in group 2, a total of 46 or 35%. The greatest number of such manifestations was in the third decade.

Certain circulatory disturbances always noted in hyperthyroidism were present. The average pulse rate was 118, 115 and 109 in groups one, two and three respectively. While there is no marked difference in these rates there is some evidence that there is a

CLINICAL AND PATHOLOGICAL EVIDENCE IN INSTANCES OF PRIMARY HYPERTHYROIDISM

INFLUENCED BY THE USE OF IODINE THERAPY

CHART VII

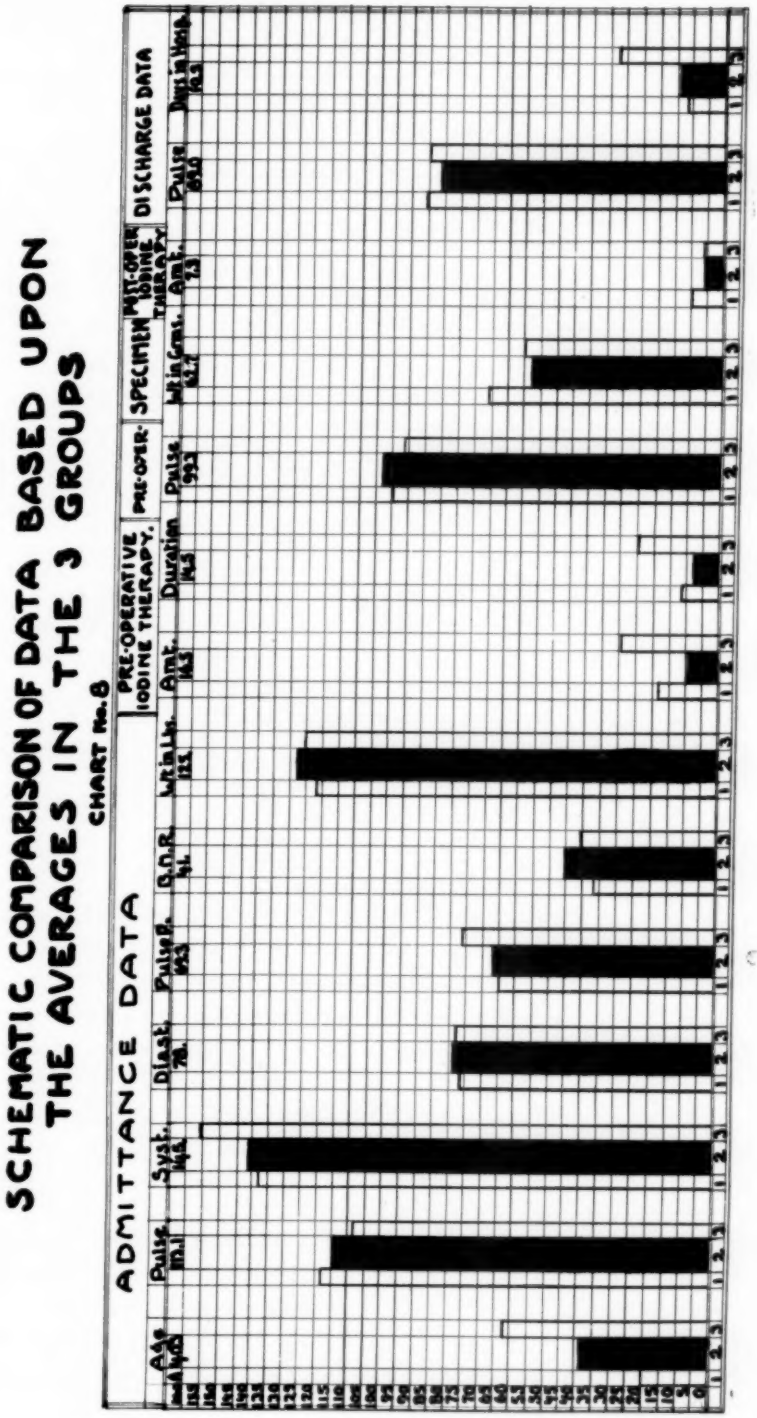
Patients Ages Ranging Above 50 Years

ADMITTANCE HISTORY											IODINE AND REST THERAPY			PRE-OPERATIVE RECORD				OP.	POST-OPERATIVE THERAPY			TIME OF DISCHARGE REC.				Acc. No.
Marital Sex	Status	Age	Chief Clinical Symptoms	P	Blood Press. Syst	Dia	P.P.	Pwr	Wt.	Lugol's Sol'n Amt.	Fre.	Dur.	T	P	R	Wt. Spec in Gm.	Fm.	Amt	Fre	T	P	R	Dys Pne	
M		55	Dif.G.I.D. Exoph.Nerv.WtvRpd.Ht.Res.	90	140	80	60	40	118	10M	TID	13	98	100	22	95	Lugl	10M	0	98	100	22	19	26103
F	M	58	Exoph.Nerv.4.WtvRpd.Ht.	100	150	100	80	30	107	10M	TID	3	99	100	20	31	Lug. Dr. Lugl	10M	TID	98	85	20	9	15049
F	M	57	Exoph. Nerv.	120	216	100	116	45	116	2M	BID	100	98	95	20	30	0	0	0		100		108	16363
M		69	Nerv.WtvRpd.Ht.Res.Dif.	100	160	85	56	12	123	15M	Dly	175	98	90	22	40	Lug. Dr.	0	0	98	80	20	182	17019
F	M	64	Nerv.WtvRpd.Ht.Wkn.	138	160	78	82	40	147	5M	TID	9	98	100	20	64	Lug. Dr. Lugl	5M	TID	98	85	20	22	16540
F	M	58	Nerv.Rpd.Ht.Res.Dif.GID.	120	107	74	33	40	107	5M	TID	3	98	100	20	32	Lug. Dr. Lugl	5M	BID	98	80	20	10	16807
M		52	Nerv.Rpd.Ht.Wkn.Enl.	120	130	85	45	30	125	5M	BID	3	98	105	20	52	Lugl	5M	Dly	98	100	20	10	15930
M		59	GID.Enl.Ankles Nerv.3.WtvRpd.Ht.Res.Dif.	110	130	60	70	50	106	5M	BID	8	98	105	25	32	Lugl	5M	Dly	97	100	20	13	15938
M		52	Nerv.WtvRpd.Ht.Res.Dif.Wkn.	80	140	65	75	35	171	5M	TID	3	98	95	25	85	Lugl	5M	BID	98	90	24	7	15431
F	M	64	Nerv.4.WtvRpd.Ht.Enl.	115	150	80	70	55	80	5M	BID	5	100	130	25	60	Lug. Dr.			98	80	22	15	15055
M		52	WtvRpd.Ht.Wkn.Enl.	120	170	70	100	94		10M	TID	4	98	100	24	123	Lug. Dr. Lugl	10M	TID	99	88	25	11	14858
M		55	Nerv.Rpd.Ht.GID.	100	190	70	110	30	137	10M	TID	7	97	70	20	42	Lug. Dr. Lugl	10M	TID	98	72	20	18	13863
M		52	Exoph.4.Nerv.3.WtvRpd.Ht.	100	150	60	90	40	135	10M	TID	4	99	72	20	105				99	96	20	20	14329
M		54	Res.Dif.Enl. Exoph.Nerv.3.WtvRpd.Ht.	110	200	90	110	38	155	10M	BID	4	97	90	22	45				98	95	20	11	14430

KEY.

CHIEF CLINICAL SYMPTOMS:- Exoph.- Exophthalmus, Nerv.- Nervousness, Wt.-- Loss of Weight, Rpd.Ht.- Rapid Heart, Res.Dif.- Respiratory Difficulty, 1,2,or3 - Degree of Res.Dif., Ankles- Edema of Ankles, G.I.D.- Gastro-Intestinal Disorders, Enl.-Enlarged Thyroid, Wkn.-Muscular Weakness.

progressive decrease in pulse rate according to increasing age. The average systolic blood pressure was 138, 141, 156 and the diastolic pressures: 72, 79, 87 in the respective groups. There is also evidence here of an increased vascular tension which is independent of the usual structural changes in the vessel walls, although the increase with the age is indicative of factors other than toxicity from thyroid overfunction. For the same reason the pulse pressure was observed to be greater in the older individuals, although the general average was high (69.3). The average positive basal metabolic rates were as follows: 37.1, 45.4, 41.4. The lowest was 8 and the highest 94. Occasional high rates were observed in the extremes of the ages, but in general they were higher in the third decade. Pregnancy, with its great metabolic demands, is probably a great factor during this period. The basal metabolic readings were the averages of several different readings at different times. There was general evidence in loss of weight, which in many instances occurred rapidly. The average weight was 125 pounds with very little difference in the averages of the respective groups. (See chart 8).


SCHEMATIC COMPARISON OF DATA BASED UPON THE AVERAGES IN THE 3 GROUPS
CHART No. 8
ADMITTANCE DATA
PRE-OPERATIVE IODINE THERAPY.
PRE-OPER.
SPECIMEN
POST-OPER. IODINE THERAPY
DISCHARGE DATA
Age
Pulse
Syst.
Diast.
Pulse P.
B.M.R.
Wt. Lbs.
Amt.
Duration
Pulse
Wt. in Gms.
Amt.
Pulse
Days in Hosp.

Preoperative treatment consisted of rest in bed and iodine therapy. The latter was always given in the form of Lugols' solution in water two or three times a day in 5 or 10 minim doses according to the judgment of one of us (Joyce) as to the toxicity of the individual patient. This is in accord with the guiding principle ordinarily carried out at the Mayo Clinic. The average amount of Lugols' solution given was 16.5 c.c. during an average duration of 14 days. Both of these averages are augmented by the inclusion of a few cases in which iodine was administered over a long period of time (180 days). When such instances are excluded the average dose becomes 7.1 c.c. and the average duration 5.9 days, although the time of treatment in several patients was only for one day. Following this preoperative treatment there occurred, as a rule, an arrestment of subjective symptoms and concomitant with such a change a decrease in the pulse rate by an average or 13.8 per minute. In some individuals (17) there was an actual increase in the pulse rate, or in others (15) it remained constant following the use of iodine. Operative procedure was instituted after a definite break in the severity of the symptoms and an established lowered pulse rate.

Double lobectomy was the surgical procedure followed. The amount of gland removed was based upon the degree of enlargement and the clinical data obtained both before and after the use of iodine. When such specimens were weighed in the fresh state it was found that the average weight in the three groups was 70.8 gm., 57.4 gm. and 50.7 gm. These weights although they represent only a portion of the gland are above the average weight (40 gms.) of the entire adult gland. The glands of group 1 were as a rule somewhat larger. In those patients who received iodine over a considerable period of time the gland tissue was more abundant and the increased weight appeared to be connected with the colloid increase. The policy of one of us (Joyce) has been to remove as much gland tissue as possible, avoiding injury to the recurrent laryngeal nerve or encroaching upon the region of the parathyroids.

The administration of iodine after the operation in some of the patients consisted in giving Lugol's solution (Lugol's 100 minims in 2% of Sod. bicarbonate and 5% glucose) by the Murphy drip method, and also Lugol's by mouth. The average amount given after operation was 7.3 c.c. In 15 instances none was given. In 34 cases one administration by the Murphy drip method referred to above sufficed. In all of the others small doses of Lugol's were given in addition to this.

It is interesting to note the length of time that these patients remained in the hospital with this combined method of therapy. We did not consider it practical or advisable to subject the patients to the determination of the basal metabolic rate during the post-operative period but we have relied upon the cessation of clinical symptoms and the constancy of a lowered pulse rate. Discharge of the patient from the hospital was considered as safe when the pulse rate remained below 100 under varying conditions and the healing of the wound was uneventful. In this series the average

period of hospitalization was 19.3 days. This average was 11.6 days after correction because of other complication in a few of the cases.

Pathological examination of the portions of the glands removed, revealed all of them to be free from nodules with the exception of three, in which there were small solitary foetal adenomata of no consequence. The glands were, in general, variable in consistency and color. In only a few instances was there the usual ischemic, fleshy, colloid free type of gland so commonly observed in hyperthyroidism prior to the present regimen which is being followed by the preoperative use of iodine.

The capsule and supportive stroma was generally increased in those glands coming from older individuals. However, in some of the specimens from the younger patients marked diffuse fibrosis was noted. The basis for such an increase probably lies in the irritation hyperplasia of connective tissue associated with cyclic functional hyperactivities and recessions, and is probably proportionate to the degree of such changes. In older individuals there is added to this the influence of circulatory deficiency because of arteriosclerosis. Except in a few instances colloid was always visible. In some cases (those given iodine over a long period of time) it was abundant. A general increased translucency of thin sections was observed. The surfaces made by sectioning were generally pinkish red and diffusely mottled with greyish specks or small poorly defined blotches. In none of these glands was there gross evidence of cystic degeneration. Vascularity was less prominent than in the glands in which iodine was not used. All in all the gross appearance of the thyroid, after iodine administration as compared to those removed without its pre-operative use, is similar to the lung in broncho-pneumonia when compared with that of lobar pneumonia in the stage of gray hepatization.

With the above clinical facts and gross pathology in mind, a detailed study of the histologic changes in the different glands of the three groups was made. The selection of blocks from different parts of the gland was determined by gross variations seen by making many different gross sections of the specimen. Microscopic sections were stained with hematoxylin and eosin with the exception of a number of frozen sections which were stained with Sudan III.

Observations were made concerning the size of the acini, their colloid content, the degree and character of epithelial change, as well as the variations in the supportive stroma and its vascular channels (see chart IX). The size of the acini varied in these instances, as it always does in direct ratio to the colloid content, and at tent. The latter varied from complete absence to large coalescent masses. Such accumulations were found in 52% of group 1, 26% of group 2, and 21% of group 3. In all of these instances iodine had been given over a considerable period.

Hyperplasia and hypertrophy were in general spotty and varied in indirect ratio to the colloid content, and at times it was as marked as is seen in the glands of patients to whom iodine had not been given. In these latter

CHART IX CONCERNING LIPOID BODIES

In Selected Specimens From

The Three Groups

LIPOID BODIES

Clinical Data				EPITHELIUM														COLLOID		STROMA	
Acc.	Age	Iodine		Acinar					Intra-acinar				Inter-acinar					Lip.	Spher.	Neut.	Lip.
No.	Yrs.	amt. cc.	Dur.	Type	No.bodies	Size	Loc.	Spheroid	No.cells	No.bodies	Size	Loc.	No.	Size	Loc.			Bdy	Body	Int	Body
17265	20	3.	5	L.cu.	9	X	Diff.	1 occas.	--	--	--	--	4	X	Diff.			--	1	--	--
14211	15	13.	13	L.cu.	6	X	Diff.	--	25	S	X	Diff.	6	X	Diff.			--	--	--	--
14661	17	1.5	4	L.col.	7	X	I.P.	1 occas.	1	S	X	Diff.	4	X	Diff.			--	1	--	--
14518	19	2.0	2	L.col.	11	X	Diff. I.P.	--	6	S	X	Diff.	10	X	Diff.			--	1	--	+
17728	22	1.0	1	Col.	19	X	I.P.	--	8	S	X	Diff.	13	X	Diff.			--	1	--	+
13624	22	12.0	6	L.col.	21	X	I.P. Diff.	1 occas.	6	S	X	Diff.	8	X	Diff.			--	1	--	--
16535	25	2.0	3	L.col.	9	Y	Diff.	1-2	2	S	Y	Diff.	5	Y	Diff.			--	2	+	--
14705	22	72.0	120.	L.cu.	3	X	Diff.	--	--	--	--	--	2	X	Diff.			--	--	--	--
15312	26	48.0	16	Cu.	22	Y	Diff.	--	6	S	Y	Diff.	14	Y	Diff.			+	1	--	--
14316	29	14.0	7	L.col.	13	Y	Diff.	1 occas.	2	S	Y	Diff.	7	Y	Diff.			--	2	--	--
16458	27	2.75	4	L.cu.	9	X	Diff.	--	--	--	--	--	4	X	Diff.			--	--	--	+
16666	30	8.0	8	Cu.	9	Z	Diff.	--	2	S	Y	Diff.	6	Y	Diff.			--	1	+	--
17635	34	8.0	8	Cu.	7	Z	Diff.	--	1	S	Y	Diff.	6	Y	Diff.			--	1	+	--
14744	35	8.0	8	Cu.	11	Y	Diff.	--	--	--	--	--	7	Y	Diff.			--	--	--	--
14479	38	3.25	8	L.cu.	8	Y	Diff.	--	2	S	Y	Diff.	5	Y	Diff.			--	1	--	--
16536	40	6.0	6	Cu.	5	Z	Diff.	1-2	1	S	Z	Diff.	4	Z	Diff.			--	2-8	--	--
17569	42	10.0	5	L.cu.	5	Z	Diff.	1	1	S	Z	Diff.	3	Z	Diff.			--	1	--	--
16640	47	3.25	10	L.cu.	0-5	Y	Diff.	1	1	S	Y&Z	Diff.	4-0	Y&Z	Diff.			--	1	+	--
16199	48	2.0	2	L.cu.	4	Y&Z	Diff.	--	--	--	--	--	3	Y&Z	Diff.			--	1	+	--
16930	53	2.0	3	Cu.	7	Y	Diff.	--	1	S	Y	Diff.	0-4	Y	Diff.			--	1	--	--
14858	52	8.0	4	L.cu.	4	Z	Diff.	--	5	S	Z	Diff.	0-3	Y	Diff.			--	1	+	--
16938	59	5.3	8	Cu.	6	Z	Diff.	--	4	S	Z	Diff.	2	Z	Diff.			--	1	--	--
13863	56	14.0	7	Col.	4	Z	I.P.	--	1	S	Z	Diff.	4	Z	Diff.			--	1	--	--
17019	69	175.0	175	Cu.	9	Y	Diff.	--	1	S	Y	Diff.	3	Y	Diff.			--	1	+	--
16363	67	66.0	100	Cu.	5	X&Y	Diff.	--	--	--	--	--	4	X&Y	Diff.			--	1	--	--
16540	64	9.0	9	L.cu.	7	X&Y	Diff.	--	--	--	--	--	7	X&Y	Diff.			--	--	--	--

Key to abbreviations:- (I) Type of Epithelium: L.cu.--Low cuboidal; Cu.--Cuboidal; Col.--Columnar; L.col.--Low columnar;
(II) Size of Lipoid Bodies: X--Small and fine; Y--Medium; Z--Large and coarse;
(III) Location and Distribution of Lipoid Bodies: Diff.--Diffuse; I.P.--At Inner Pole;
S.--Solidly filled.

cases iodine in small doses had been given for a day. Fewer intra-acinar papillary projections were seen in group 1. In most of the glands studied, evidences of progressive stretching with blunting of the intra-acinar papillary projections was observed. In many cases they were entirely erased. Many acini were lined by band-like accumulations of slightly hyperplastic epithelium. The inter-acinar epithelium showed changes that varied in a manner similar to that lining the acini. In some of the instances (those given iodine for a long time) there was evidence of a marked hyperplasia and hypertrophy of the inter-acinar epithelium with the formation of numerous newly formed small acini. Such changes were generally observed in glands having either focal or general excess accumulations of colloid. (See photomicrograph No. 1). The greatest variation in epithelium was observ-

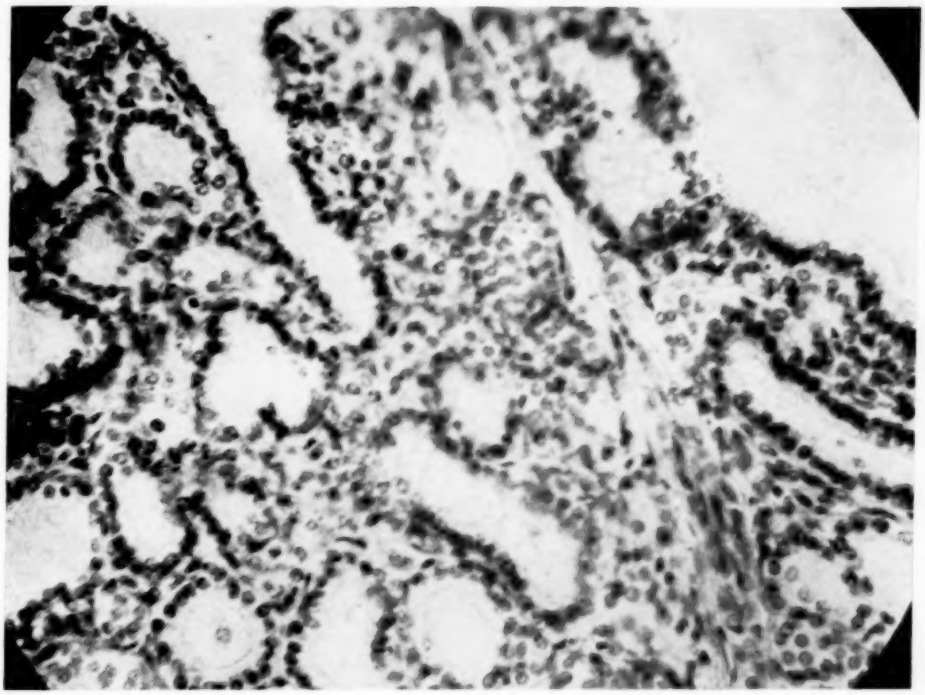


FIG. 1

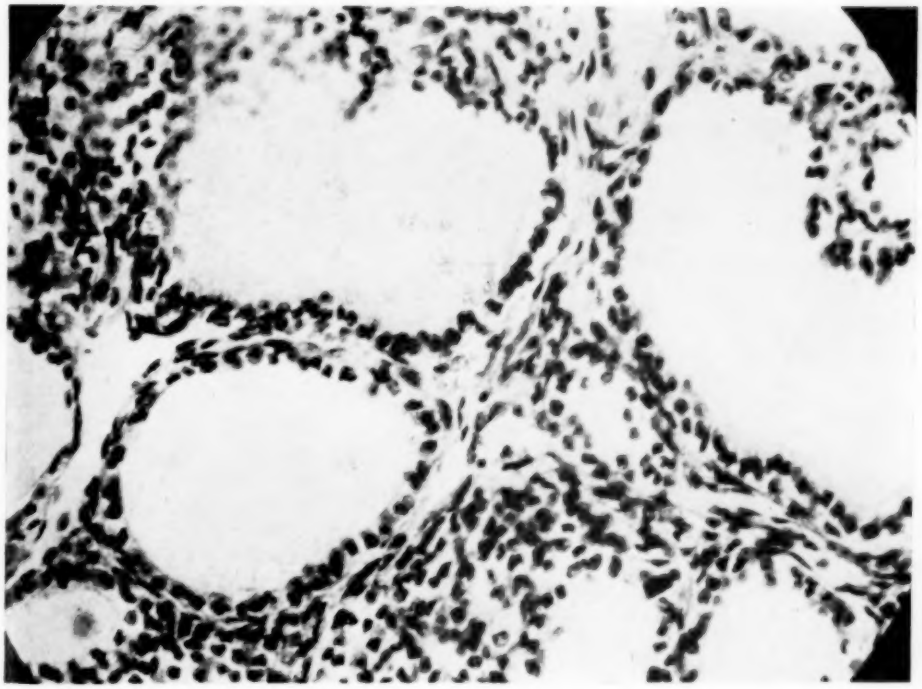


FIG. 2

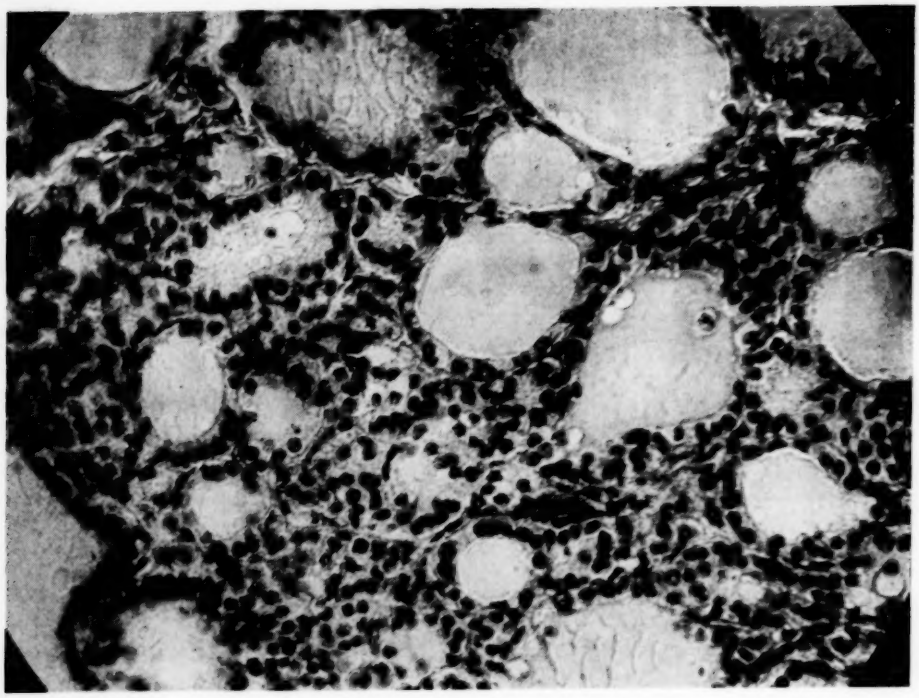


FIG. 3

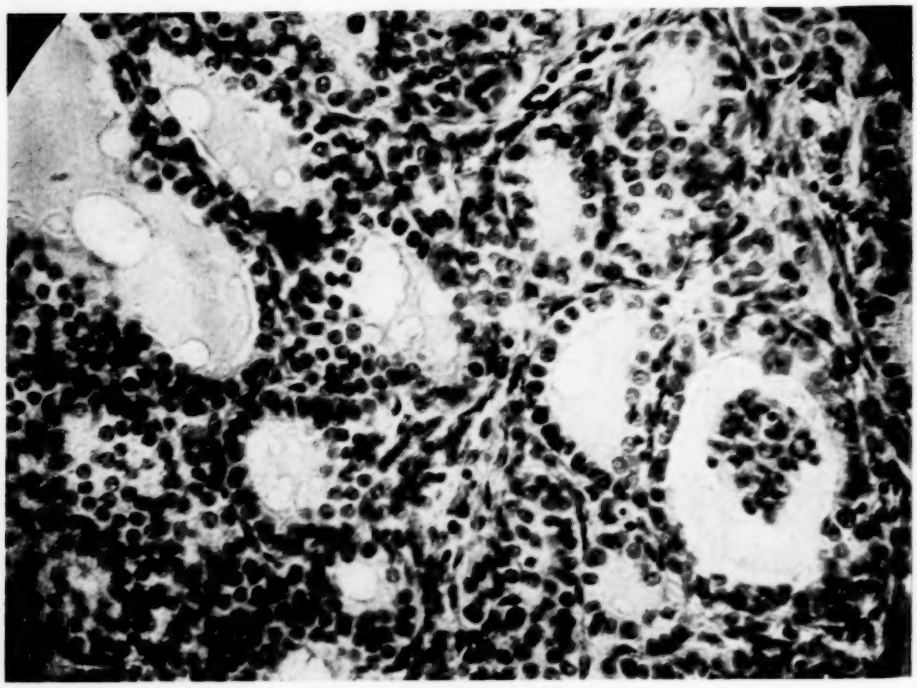


FIG. 4

ed in groups 2 and 3. A patchy stroma variation was also seen. In the glands of younger individuals fibrosis was always found at the sites of greatest hyperplasia, but it was generalized in only a few instances. A gradual reduction in the supportive stroma content was found as the inactive areas were approached. In the glands of older individuals, a definite perivascular fibrosis with marked hyaline changes was often seen. Such scarred areas were frequently observed to be fringed with numerous small acini. They generally appeared broadest about the borders of such hyperplastic areas and narrowest as they passed through regions with colloid bulging acini.

The blood vessels showed less general and considerably less focal engorgement than is commonly seen in untreated glands. Endarteritis was observed eight times (8%) in group 2 and nine times (64%) in group 3. No such changes were seen in group 1.

On the basis of such histologic studies the degree of involution was

GRADING OF ABNORMALITY IN SPECIMENS OF INSTANCES OF HYPERTHYROIDISM ON THE BASIS OF THE DEGREE OF INVOLUTION
CHART X

Age Limits	No. of Cases	Groups	Grade I	Grade II	Grade III	Grade IV
0 - 25	17	1	6	6	5	0
26 - 50	100	2	32	45	23	0
51 +	14	3	3	8	3	0
Total	131		41	59	31	0

So-called round cell infiltration was not found to be extensive. This too was found to be spotty in its distribution. It was much less frequent in group 1 than in groups 2 and 3. These lymph cells did not seem to vary from their usual character or distribution. Pseudo-lymph nodes were found two times in group 1, 30 times in group 2, and not at all in group 3.

The estimation of the degree of lymph vessel dilatation is somewhat more difficult. Sometimes these channels were widest in the areas of increased activity, and other times they appeared to be actually obliterated by the pressure of cells on their walls. estimated and the specimens were graded, as to the extent of the abnormality that was evident (see chart X). In grade 1 there was sufficient involution so that the nearest approach to normal was observed, while in grade 4 the conditions would be similar to those seen in untreated glands. (See microphotographs 2, 3, 4). Aall of the 131 examined had undergone some degree of involution. One hundred (76%) of all of these showed at least 50% reversion on the basis of histologic changes. While this study was in progress Sager (vide supra) published a similar method of grading the pathological changes.

Recently Jaffe (15) has brought to our attention certain histologic studies concerning the lipoid bodies of the thyroid. He observed a gradual increase in number and size of such granules up to puberty, and pointed out that its influence later in life had not been established. Varying notions of the significance of such lipoid content have been advanced, namely (1) that it may be related to cell waste products, (2) that it originates from desquamation of epithelium and (3) that it is an actual secretory substance. Jaffe concluded that the excretion of lipins starts after the first year of life and increases with age. Also that they are products of secretory activity of the epithelium and are discharged into the colloid where they are dissolved. In addtiion he found a Sudan III staining substance in the plasma.

(15) Arch. Path. & Lab. Med., 3:955-962 (June) 1927.

It seemed of interest to study the results obtained by stained sections (Sudan III) from selected instances (26) with ages ranging from 15 to 69 years, under the influence of varying amounts of iodine (see chart XI). The lipin content of the epithelium, colloid and stromas was noted.

The number of lipin granules in the acinar epithelium varied from 5 to 22 in the different instances. They were most numerous in the glands of individuals below the age of 35. The granules were largest in the glands of older individuals. They were diffusely scattered through the cells. Spheroid bodies were only occasionally found in the colloid. A much smaller number of lipin granules were found in the desquamated intra-acinar epithelium. They were generally larger but similarly distributed. The granules in the inter-acinar epithelium were generally somewhat larger and varied from 2 to 14 in number. No lipins were seen in the colloid. A small number of spheroid bodies were seen here. Most of the interacinar blood vessels contained sudanophil plasma. No sudanophilic substance was seen in the lymphatics.

The results of this study are in agreement with those of Jaffe (16).

(16) Arch. of Path. & Lab. Med., 5:13-22, Jan., 1928.

We observed that the size of the granules remained somewhat larger in older individuals in instances of exophthalmic goiter just as they do in normal thyroids of corresponding age. In these instances the amount, duration, and method of iodine therapy appears to have played no specific role in influencing the size, character, and distribution of lipins, except in so far as it produced a recession of activity and established stability of epithelium. The disappearance of fat from the supportive stroma was most likely due to generalized increased metabolism. The sudanophil content of the blood vessels and the absence of any stainable substance in the lymphatic channels may possibly point to the manner of dispersion of the hormone. Especially if one can assume that the presence of lipins in the various types of functioning cells are associated with hormore production.

Discussion

It is noteworthy that in this series of primary hyperthyroidism, there appears to be an increase in the number

HISTO-PATHOLOGY GROUP I

Acc. No.	Iodine amt.cc	ACINI Size		Colloid amt.	Colloid Cond.	Epithelial Hy-pl. F.	Hy-pl. G.	Hyp-tr. F.	Hyp-tr. G.	Inf. F.	Inf. G.	STROMA Increase F.	Increase G.	Round Cells F.	Round Cells G.	Round Cells Nodes	Lymph V. Dil. F.	Lymph V. Dil. G.	Blood V. Eng. F.	Blood V. Eng. G.	ARNOR. Degree
14581	2	M	S	FA GS	GH LV	2	0	0	2	0	0	2	3	2	1	0	2	0	1	0	2
17728	1	S U		FA	LV FKI	4	2	4	2	3	0	0	1	2	2	0	3	0	2	0	3
14186	4	L U	S	FA LCYS	LV GH FKI	3	0	4	0	3	2	3	1	2	0	2	2	0	1	0	3
13624	12	L U	S	FA LCYS	FV GH FKI	2	0	4	0	1	0	0	2	3	1	0	2	0	0	0	2
13663	24	S	L	FA LCYS	LV FKI	2	3	0	3	3	0	4	3	0	2	0	2	0	2	0	3
13908	14	S	L	S A LCYS	GH	1	0	1	0	0	1	0	2	0	1	0	1	0	1	0	1
14211	13	S	L	A LCYS	FV GH FKI	2	0	2	0	1	0	2	1	2	0	0	1	0	1	0	1
15569	8	M	S	S	FKI	0	2	0	2	1	1	4	2	4	1	0	3	2	3	2	3
17715	5	S	M	M	GH	1	0	2	0	1	0	2	0	1	0	0	2	0	1	0	1
13568	10	S	L	LCYS LF	FV	1	0	2	0	2	0	2	0	4	0	2	1	0	0	1	1
17302	3	S	M	M	GH FKI	1	0	1	0	0	0	2	1	1	0	0	0	2	2	0	1
14047	4	S	L	A LCYS LF	GH FKI3	2	0	2	0	0	0	3	2	2	0	0	1	0	1	0	1
14705	72	S	L	A LCYS LF	GH FKI3	3	0	3	0	2	0	3	0	1	0	0	2	0	1	0	2
14661	1.5	S U	S	S FA	FV	2	1	3	3	0	0	2	1	3	2	0	2	0	0	2	2
16535	2	S	S	S FA	FV	3	2	3	2	3	2	4	3	2	3	0	0	3	0	2	3
15055	20	S	L	A LCYS	FV GH FKI	2	0	3	1	2	0	3	2	1	0	0	2	0	1	0	2
17265	3	S	M	M FA	FV GH FKI	2 S	0	2	0	1	0	2	0	0	0	0	2	1	2	1	2

Chart IX. Illustrating the manner of study of all of the 131 instances. Similar charts of groups II and III are not included in order to conserve space.

Key to abbreviations:-- (I) Size: L--Large; M--Medium; S--Small; U--Undifferentiated;
(II) Colloid: (A) Amount: S--Scant; M--Moderate; A--Abundant; LCYS--Cystic dilatation of acini--large cysts; FA--Focal absence; FC--Focal collections; LP--Large pools--(Acini ruptured);
(B) Condition: FV--Focal vacuolisation; GH--Generally homogeneous; FKI--Focal epithelial implusions;
(III) Epithelium: (A) Hy-pl.--Hyperplasia; F 1,2,3,or 4--Focal and Degree; G 1,2,3,or 4--General hyperplasia and degree; FS--Focal solid;
(B) Hyp-tr.--Hypertrophy; F 1,2,3,or 4--Focal and degree; G 1,2,3,or 4--General and degree;
(C) Inf.--Infolding; F 1,2,3,or 4--Focal and Degree; G 1,2,3,or 4--General and Degree.

developing at an earlier age than has been previously observed by us. Whether this is due to over use of iodine given prophylactically or therapeutically was not learned from our records. There is a suggestion that such injudicious uses may play a role. On the other hand it is our experience that the extreme degrees of toxicity are less frequently found since an attempt has been made to establish the required amount of iodine in the food content. Yet Liek (17) and others

(17) Müncher Med. Wochenschrift, 74:1786 (Oct.) 1923.

seem to think that endemic goiter is increasing by such prophylactic use of iodine. In this clinicopathological study we were, however, concerned with the possible effect of iodine as a prophylactic agent in goiter prevention only in so far as it may have induced hyperthyroidism for which we now

use iodine in the therapy or in so far as it may modify such action from a clinical standpoint.

The clinical changes accomplished by the use of iodine in carefully selected instances of primary hyperthyroidism are generally recognized. They consist of a temporary abeyance of most of the usual manifestations with the exception of the exophthalmos which persists for a considerable period of time and often remains permanent. The pulse rate drops, the basal metabolic rate decreases and the nervous symptoms become less. This improved clinical state varies in degree and time, but is usually of short duration.

Opposition to the use of large amounts of iodine in the therapy has been expressed by a number of writers. Marine (vide supra) spoke sarcastically of the utilization of massive doses as the "iodine flood". In our procedure the average daily dose was 152.9 mgm., an amount in excess of that recommended by Marine. We were not able to establish any serious effects of such doses over a short period of time after a most careful clinical and pathological study. In most instances the amount of iodine used actually appeared to give definite clinical results. It may be true, however, that smaller amounts given over a more carefully determined period might give more permanent results. It seems to us that this effect of iodine dosage in a specific instance depends upon the status of the gland at the time it is administered. As has been previously pointed out the thyroid undergoes varying degrees of remission and progression in its activity and that the clinical symptoms of hyperthyroidism lag during these cyclic changes. Therefore the effect of the administration of iodine will depend upon the extent of the natural involution already in progress and variable dosages will under such conditions produce dissimilar effects. Inasmuch as the role of iodine is apparently concerned with intra-acinar colloid accumulation much depends upon the direction of the polarity of the cell at the time the iodine reaches the gland. It follows that if colloid storage is already in progress less iodine would be required than if the progressive secretory momentum of cells were still to be overcome. So that since it is impossible to accurately determine the exact secretory state of the gland, large doses may actually increase the negative phase of areas undergoing inversion, and have a diminished effect upon areas that are still irritably hyperplastic or leave them uninfluenced. The foregoing is of course an assumption based upon the idea that the action of iodine is largely a matter of physical chemistry stimulating colloid production and by secondary increased intra acinar pressure, ironing out the hyperplastic infolding, and finally inhibiting the secretory power of the epithelium. On the other hand massive doses may abruptly halt the secretion and determine a properly timed surgical intervention.

Following iodine therapy the amount of the gland to be removed still remains a question of symmetry and the individual surgeon's judgment. It is necessary from the surgical point of view, in these cases of primary hyperthyroidism influenced by iodine, to take

into consideration several factors: (1) The age of the patient; (2) The duration of the condition; (3) The severity of the symptoms; (4) The amount of iodine given, and the rapidity of response to it; (5) The fact that a certain amount of hyperplasia will recur in the remaining stumps. It has been our policy to wait for the stabilization of clinical symptoms and then remove as much as possible in order to avoid recurrences. In a considerable number (8 to 10%) there may follow a period of hypothyroidism but at the time of operation this occurrence cannot be foretold so that its possible development must be temporarily ignored. The postoperative excess hyperplasia was controlled with further small doses of iodine, the postsurgical effect of which has been pointed out by the experiments of Halstead (vide supra), Marine (vide supra), Loeb (18) and Else (193. The temporary hypothyroidism was counteracted by the use of dessicated thyroid. The end results of such a detailed rationale in the therapy can only be determined by a careful follow-up record of patients so treated. This phase of the study is being continued.

(18) J. Med. Res. 40:199-265, July, 1919.
(19) J. A. M. A., 89:26, 2153 Dec., 1927.

In recent studies of the pathological changes produced by iodine in instances of primary hyperthyroidism Cattell (20), Giordano (21), Sager (vide supra) and Rienhoff and Lewis (22) and others have in general agreed upon the effect of iodine, namely, that it causes a recession of activities with the accumulation of colloid and a general reduction in the vascularity. Microscopically the essential changes noted have to do with progressive development of intra-acinar colloid with a pushing back of the hyperplastic projections and the establishment of more uniformity in the size and regularity of the acini. Similar changes were found by one of us (Menne) in the glands of this series. There was no consistency in the relationship of the changes to the amount of iodine administered. In general the longer iodine was administered the greater was the accumulation of colloid. But in some instances in which iodine was used for a single day, large pools of colloid were seen. These were probably remnants of a previous state of inversion. On the other hand in some of the glands of patients treated with iodine over a long period of time (175 days) discrete hyperplastic foci occurred. In these instances, collections of small acini with hyperplastic epithelium were observed lying between those bulging with colloid. This may be assumed to be a response, on the part of the gland, to stimuli for more hormone, in the presence of the depressing effect of iodine produced colloid storage. Round cell infiltration is so variable in its character and distribution that its real significance cannot be determined, except that it may be concerned with removal of the biproducts of cell metabolism in the fabrication of the hormone or accompany a more definite chronic lymphangitis.

(20) S. Clin. N. Amer., 6:597, 603, June, 1926.
(21) Arch. Path. and Lab. Med., 1:881-888, June, 1926.
(22) Arch. of Surg., 16:1, 79, Jan., 1928.

No marked variation in the histopathology occurred in the three groups

and there is no particular advantage in such a division. Beneath the various patterns resulting from primary hyperthyroidism influenced by varying amounts of iodine in the therapy, one can still see evidence of the usual physiologic spotty activity, the changes induced by remissions and progressions following unusual demands, and the scars wrought by advancing age and other diseases. The full role of iodine, while illuminated by the work of Kendall and Harrington as to its specificity in the hormone, still remains hidden in the mass action evidenced in its valuable clincal use.

Conclusions

(1). The effect in an endemic area of iodine in the therapy of primary hyperthyroidism occurring in patients over a wide age variation (15 to 69 years) is given.

(2). The study of such instances according to groups based upon age and the periods of puberty, adolescence, menopause and post-menopause, while interesting offers no particular advantage. The essential differences between the clinical and pathological manifestations in these three groups are not marked.

(3). An increased vascular tension irrespective of age or arterial disease is evident.

(4). The clinical symptoms of primary hyperthyroidism in general are less severe since the prophylactic use of iodine, while there is some evidence of an increased number of cases requiring supervision and observation.

(5). Iodine in the therapy temporarily allays the symptoms and stabilizes metabolism, but is limited in maintaining such a balance.

(6) Massive doses followed by properly timed surgical interference have given satisfactory immediate results, but the permanency and real value require a follow-up study.

(7). It is advisable to remove as much gland as possible and to control the temporary postoperative hypo-or hyper-activity with well chosen doses of dessicated thyroid or iodine respectively.

(8). The average amount of the gland removed in this series exceeded the average weight of the entire adult gland.

(9). The gross and histologic changes found here are in accord with those of other investigators. Intra acinar colloid storage with a physicochemical and mechanical inhibition of secretory function and power is probably as important as an explanation of iodine action as the complete iodinization of the hormone.

(10). The nature and distribution of sudanophilic substance suggests a marked cellular metabolic disturbance associated with hormone fabrication.

(11). On the basis of the histologic study it was possible to determine that all of the glands had undergone some change. In 76% of the glands at least a 50% inversion occurred following the preoperative use of iodine.

(12). The permanency of the efficacious use of iodine can only be determined by more experimental studies of its real role in colloid storage and checking of the metabolic constancy of patients so treated.

Editorial

The Spread of Broad Tapeworm Infestation Throughout the United States

Within the last twenty years there has occurred a most interesting increase in the incidence of broad tapeworm (*Diphyllobothrium latum*) infestation throughout the United States, to such an extent that this parasite must be now regarded as of both medical and economic importance in this country. In 1895 very few human cases of infestation with this tapeworm had been seen in America, and such clinical rarities were confined to their occurrence in immigrants from the Baltic region, Finns especially bringing with them from their homeland one or more specimens in their intestines. Wherever a large aggregation of Finnish immigrants was concentrated, specimens of this worm were sooner or later reported. In Michigan, particularly, the large Finnish population in the Copper Country provided numerous specimens of this worm. For some years these specimens were all naturally regarded as imported in the bodies of their hosts. Since known infestations extending over fourteen years had been reported from Europe, it was not considered safe to regard this infestation as indigenous until the parasite was found to be harbored by a native-born American. That such indigenous cases must sooner or later appear seemed inevitable. The stage was fully set for the appearance of native Americans infested with the broad tapeworm, and who, never having been out of their native land, had acquired the parasite at home. The large body of Finns in the Great Lakes Region who must harbor the fish tapeworm, since they came from a country in which such human infestation with this worm is variously estimated at from 20-40 per cent; the discharge into the waters of the Great Lakes of sewage containing great numbers of ova of this worm, and the favorable conditions for the life and development of these ova into free-swimming embryos and their plerocercoid stages in the fish of these lakes made it no difficult or improbable prophecy, as early as 1897, that this parasite was certain to become indigenous in these waters. By 1911-12 this had already occurred. Native cases had already been reported from Minnesota and Michigan. Then in 1911-12 fish obtained from Portage Lake examined at the Pathological Laboratory of the University of Michigan were found to have typical fish tapeworm plerocercoids in them, and the fact that this parasite had established itself in American was demonstrated. Since that time an increasing incidence in the number of specimens of the broad tapeworm sent into various pathological laboratories throughout the country has occurred. Not only is this

true of the Great Lakes region, but personal communications from laboratory men in the East, particularly in New York, bear this out. In one large diagnostic laboratory in the latter city, it is stated that fifty per cent of the tapeworms brought in are now of the broad form. Of still greater interest is the fact that today most of the infested patients are native Jews, instead of the Finnish or Swedish patient of 15-20 years ago. In Michigan the broad tapeworm cases now come from the industrial towns in the lower portion of the state, instead of from the Upper Peninsula as they formerly did. Detroit now furnishes the great majority of these cases, and the patients so infested during the last five years have all been Jews. This opens up new and very important lines of investigation. It is very evident that fish infested with the broad tapeworm are now in the markets of our large cities, and that the consumption of these in an uncooked or imperfectly cooked state must be responsible for the increasing incidence. It is, therefore very important to discover the source of these infested fish, and to issue proper warning as to their use. As far as some of the cities are concerned, the majority of the fish appearing in the markets are from northern lakes; and in the case of pike and pickerel are brought in from Canadian waters. Lake Winnipeg has been shown by Magath to be another endemic focus of infestation of the fish. It is interesting that the fish brought to the large markets for the Jewish trade are brought in unfrozen, and are used for food uncooked. Such fish sell at a certain premium as far as the Jewish trade is concerned. We are, therefore, in possession of all the links in the chain of knowledge explaining the increase in the incidence of human infestation with this parasite, and the change in the racial type of host, from Finn to Hebrew. As to the species involved the plerocercoids have been found chiefly in pike, pickerel and burbot. The last named is not likely to appear in the markets; of the others the walleye pike is probably the most common source of the infestation. No plerocercoids have been found in white fish. Nevertheless, the safest rule will be to eat no fish from northern lakes that have not been thoroughly cooked. Educational warnings should be given against the eating of raw fish. Salting, drying and ordinary curing do not kill the plerocercoid. As to the injurious effects in the host of the broad tapeworm a marked individual susceptibility must occur. In Finland only a small percentage of those harboring the adult tapeworm show any well-marked clinical symptoms. These are of the nature of an anemia, which may vary greatly in degree, from that of a simple secondary anemia to severe types resembling pernicious anemia. After expulsion of the worm recovery is usually rapid and complete. It is also of importance to know that liver diet results in rapid restoration of the blood picture to the normal, even when the worm is still present in the intestine. The pathology of fatal cases presents the picture of a severe hemolytic anemia, practically identical with that of pernicious anemia, except in the tract degenerations of the spinal cord. Glossitis, hemosiderosis of liver and other organs, marked atrophy of the mucosa of stomach and intestine.

fatty degenerative changes in myocardium and liver, with megaloblastic or exhausted bone marrow are found in the severe cases. Every case of anemia coming for treatment should have careful and repeated stool examinations made for ova or segments of this worm. The percentage of infested cases without symptoms to those showing anemia is high, so that to every infested patient with the latter symptom there are many who have the worm but present no symptoms (1-2 per cent only of those infested show anemia according to Faber). Treatment is easy and simple. It must be borne in mind that often more than one worm is present, and that careful search should be made for the head or heads. It is unfortunate that such a parasite should have been allowed to become established in this country. The proper disposal of sewage from our towns and villages would, in the first place, have prevented such an infestation of our food fishes, but in the existing stage of our civilization such was an impossibility, so, although cognizant of the situation and its possibilities, we have been obliged to wait and see slowly but surely realized the fulfillment of the prophecy made more than thirty years ago. As in so many other instances our knowledge outruns our ability to act upon such knowledge.

Abstracts

Sex-Differences in Heart Action. I, Duration of Systole; II, Heart Rate. By W. P. Lombard and O. M. Cope (Amer. Jour. of Physiology, December, 1927).

An examination of the curves of the duration of systoles in men and women, in recumbent, sitting and standing positions, with respect to cycle lengths, these being plotted as abscissae and systole lengths as ordinates, show that systoles in all positions progressively shorten as cycle lengths decrease. As cycle lengths shorten (pulse rates increase) not only is there less time for venous blood to accumulate, but the blood is pumped out of the veno-auricular reservoir more rapidly, and the systoles become shorter and shorter as the cycles decrease. The systoles are longer in the recumbent position than in sitting, and in sitting than standing, for like cycle lengths, because gravity retards the flow of venous blood in increasing proportion as the position approaches the horizontal. The relative pitch of the three curves indicates that as the cycle lengths decrease the systoles shorten less rapidly, also as the position becomes more horizontal. In long cycles (slow rates) there is time for the blood to get back to the heart in spite of the retarding effect of gravity in the standing and sitting positions; but as cycles shorten, gravity has a relatively greater influence, and although the effect of short cycles on the accumulation of venous blood is to be seen in all positions, it is more marked in the sitting and still more so in the standing curve. Although the curves of men and women show that the systole lengths respond in general in like manner to the effects of heart rate they respond in different degrees. The systoles of women are longer than those of men for like cycle lengths in all positions. The rate of the fall of the curves of women is different from those of men and this difference varies with the position. It is suggested that the difference between the sexes may be due to the hearts of women being smaller in comparison with their size than those of men. If this is true it would explain why the effects of gravity and of changes in cycle length would be greater in the case of women than men. The study of the heart rate in men and women shows that women's hearts beat faster than men's in all positions studied. The pulse of women does not slow as much as that of men as the position becomes more horizontal. Differences in rate between men and women are greater as the rates compared are more rapid. The systoles of women are uniformly longer than those of men at the same cycle length and position. The systoles of women do not lengthen to the same degree as those of men as the position approaches the horizontal. The greater the difference in the pulse rate of women as compared with men, the less is the difference in the length of the systoles. As cycles lengthen, the systoles of men lengthen more than those of women, and the pulse rates decrease more, except in the case of the recumbent position in which the rates are all very slow, and so approach each other. As the position approaches the horizontal, the lengthening of systoles and decrease of pulse rates are in both cases greater for men than women. The explanation of these differences in pulse rates in the two sexes, as in the systoles lengths, may be that the hearts of women are smaller in proportion to the size of their bodies than those of men. The hearts of women maintain a higher rate to compensate for the larger amounts of blood they have to pump in relation to their size. The hearts of women compensate for their sex-difference either by a relative increase of rate or a lengthening of the systole. The faster pulse rates of women are accompanied

by relatively longer systoles, and it suggests itself that these faster rates constitute a compensatory phenomenon, which shortens the systoles of women.

Two Years' Experience with the Malarial Treatment of General Paralysis in a State Institution. Clinical, Serological and Autopsy Observation in 100 cases. By Max A. Bahr and W. L. Bruetsch, Central State Hospital, Indianapolis, Indiana (Amer. Jour. of Psychiatry, Vol. VII, March, 1928, p. 715).

Of 100 general paralytic patients treated with malaria, 25 were able to leave the hospital. Twelve patients improved to such a degree that they can be trusted in an useful occupation in the hospital. Forty patients are placed in the unimproved group. In 32 patients of the latter group the disease is progressing. In 8 instances the disease has remained stationary. Five patients succumbed during the rigors and 18 died following the malaria. Serological changes following malarial treatment occurred in both the improved and the unimproved groups. While there was no parallelism between the degree of clinical and serological improvement, particularly as far as the colloidal gold curve was concerned, it was higher in the improved groups. The paretic gold curve was reduced in intensity but remained of the paretic type. Then conversion of a paretic curve into a true luetic one in our cases was an exception. The method of the treatment of general paralysis with malaria is relatively simple, compared with the other methods and can be easily carried out in a state institution. It cannot be denied that this form of treatment is attended with definite risk for the patient. With a better knowledge of the complications that arise during the rigors, death due to therapeutic malaria will be reduced. If, on the other hand, one reviews the fatalities occurring in the course of the specific treatment, particuraly with the intraspinal methods, one is aware that no treatment is without hazard. Of the five patients who died during the malaria, the immediate cause of death in two cases was malaria, one died of splenic rupture, one developed a pneumonia, and in one instance death was caused by paralytic seizures. In the 18 cases dying following the malaria, death took place from 2 weeks to 18 months after the treatment. Those who died shortly after the treatment (2 weeks to 2 months) were advanced cases of over 2 years standing. Those patients did not recover from the malaria, they failed to regain the weight which they had lost during the rigors and were rapidly going down-hill after the cessation of the malaria, some with the development of trophic ulcerations. In these advanced cases it seemed that death was hastened by the inoculation. In some instances a slight physical improvement was noted. This was only of a short duration and not accompanied by a mental improvement. Two cases of this group deserve notice, one, a paralytic, who died of a splenic abscess 7 weeks after the paroxysms were stopped, and the other was a patient inoculated from this case, who showed at autopsy a verrucose endocarditis of the mitral valve, hemorrhagic infaraction of the spleen and areas of embolic softening in the brain. This case shows clearly that the present method of direct transmission of blood from patient to patient is not without danger, as the donor may be the carrier of latent disease germs which may be transferred together with the malarial plasmodia. To avoid such unfortunate accidents the more complicated method of inoculation by Anopheles as elaborated by English authors could be employed.

The Active Principle of the Posterior Lobe of the Pituitary Gland. I, The Demonstration of the Presence of Two Active Principles; II, The Separation of the Two Principles and Their Concentration in the Form of Potent Solid Preparations. By Oliver Kamm, T. B. Aldrich, I. W. Grote, L. W. Rowe and E. P. Brybee (Jour, of the Amer. Chem. Soc., 50, 573, 1928).

The manifold physiological activities of extracts of the posterior lobe of the pituitary gland are now well known: namely, their effect in stimulating uterine contractions (oxytocic activity), their ability to raise the

blood pressure (pressor activity) and their diuretic-antidiuretic effects (renal activity). These three types of activity have led the way to three definite and important medical applications; these are illustrated respectively by the use of pituitary solutions in obstetrics, in the treatment of surgical shock, and in the control of diabetes insipidus. On the other hand, chemical information concerning the physiologically active constituents of pituitary extracts is rather meager; in fact it has not been shown definitely whether the above enumerated pharmacological activities are due to a single chemical substance (hormone) or to the presence of several different compounds. The American investigators, and this is true especially of the Johns Hopkins and the U. S. Hygienic Laboratory groups, have defended the evidence favoring a single active principle, whereas the English workers have argued for two or three principles, while the Germans at one time claimed the separation of even a larger number. The present investigation has been successful in obtaining two fractions differing from each other when subjected to the two acceptable quantitative assay methods; these two principles have been obtained in the form of stable, highly potent, water-soluble powders. By recombining the fraction in the original proportions a pituitary solution indistinguishable from the original is again obtained, thus proving that no injury of any active principle has taken place. The authors summarize their work, as follows: The posterior lobe of the pituitary gland contains two important active principles; one which raises blood pressure and another which stimulates contraction of uterine muscle. A substantially complete separation of these two active principles has been accomplished by the employment of salting-out methods, and, subsequently, by the use of appropriate solvents and precipitants. Solutions of these separated active principles have been recombined to form a pituitary extract identical with the original from which they were prepared, thus proving that no decomposition has taken place. The substantially pure pressor principle (B-hypophamine) has been obtained in the form of a white, stable, water-soluble powder 80 times as potent as the International Standard Powdered Pituitary. The separated oxytocic principle (A-hypophamine) has been obtained in the form of a white, stable, water-soluble powder which is more than 150 times as potent as the International Standard Powdered Pituitary. The pressor principle has been found to be responsible for the diuretic-antidiuretic action of pituitary extracts. The pressor principle when tested on animals for demonstration of pressor effects shows the development of tolerance which is characteristic of active pituitary extracts. It has been shown to possess no appreciable depressor action. Both active principles are basic bodies presumably amines. Practical manufacturing methods have been developed for the separation of these two hormones, and they have been made available to the medical profession for careful clinical trial. As a result of this preliminary work the foundation is now laid for an investigation of the chemical nature of the separated hormones of the posterior lobe of the pituitary gland, together with a more exhaustive study of their pharmacological properties. While additional purification may raise the potency values above those reported here, and it is probable that ultimately these two principles will be secured in crystalline form, such purification is not essential to the successful clinical application of these two new products.

Reviews

The Diagnosis of Congenital Cardiac Disease. Part I, The "So-called Acyanotic" Cases, By Maude E. Abbott, M.D., and Edward Weiss, M.D., Philadelphia; Part II, True "Morbus Caeruleus." By Maude E. Abbott, M. D., McGill University, Montreal. Blumer's Bedside Diagnosis, II, 353-514. W. B. Saunders Co., Philadelphia, 1928.

A thorough knowledge of congenital cardiac anomalies is essential to every internist, for, no matter how infrequent these lesions may be, if one is to stand on safe ground in the differential diagnosis of heart disease, he must have an understanding of the circulatory and respiratory phenomena associated with such disturbances of development of the heart. Such an understanding has a practical clinical value far out of proportion to the relative frequency of cardiac anomalies. The study of the circulatory and respiratory signs and symptoms produced by such defects, which are the result of the interaction of simple physical laws, gives a knowledge essential to a solid foundation in the broader field of general cardiology. There is probably no part of cardiac pathology, symptomatology and prognosis so little known to the general practitioner as that of congenital heart disease, and many cases of such go unrecognized or incorrectly interpreted. This failure is, of course, of immense importance to the unfortunate patient, and this is particularly true of that larger and clinically much more important group of congenital cardiacs who possess anomalies giving slight or latent symptomatology, but compatible with a relatively good expectancy of life provided they do not meet with accidents or intercurrent complications precipitating a breakdown at the site of cardiac weakness and strain. The number of these congenital potential cardiacs is probably very much greater than is usually supposed, and preventive medicine is concerned with their early recognition and the proper preventive care that should be accorded to every potential cardiac case. Up to very recent years the average treatment of the subject of congenital cardiac lesions in textbooks of internal medicine has been very unsatisfactory, and the clinical differentiation of the different types unnecessarily obscure. The average internist avoids the paragraphs bearing upon congenital cardiacs as nuisances too rare and unpractical to be worthy of consideration or understanding. He will waste no time upon them. This attitude of mind is true to some extent even of some of those who pose as cardiologists, or at least, lay claim to a more superior knowledge of cardiac disease. Therein a fundamental error is committed; for the problems of cardiac congenital lesions are mechanicophysical ones, embracing the whole fundamental anatomy and physiology of the circulation; and the elementary knowledge of the normal development of the heart, its normal anatomical structure and its normal physiology makes understandable the deviations due to prenatal disease and disturbances of embryonic development. The difficulty which most physicians have of visualizing the anatomical changes and the resulting disturbances of the circulation will disappear with a knowledge of the anatomical nature of the defect and its resultant disturbance of the circulation. This knowledge is concentrated in Dr. Abbott's book as it is in no other work on the heart. A clear picture of the possible anatomical condition existing is given, and then a logical classification of the various clinical types of congenital cardiac disease. This classification is based upon the pathologicophysiological conditions of the circulation imposed upon it by the new conditions produced by the defect. In this clinical classification Dr. Abbott follows Bamberger who taught

that cardiac anomalies should be classified according to the presence or absence of mechanical interference with the oxygenation of the arterial blood, that is, the presence or absence of congenital cyanosis. From this point of view three classes of congenital heart lesions may be recognized: I, the Acyanotic Group, comprising such cases as coarctation of the aorta and other left-sided lesions in which no abnormal communication between the two circulations exists, and in which, therefore, there is no cause for congenital cyanosis; II, Cyanose Tardive, cases in which a communication does exist, in the form of a localized interauricular, interventricular or aortic septal defect or a patent ductus arteriosus, but without other complication, so that under the normal conditions of the circulation, in which pressure is higher on the left (arterial) side the intracardiac or intra-arterial current is of the nature of an arterial-venous shunt. Here there is also no reason for cyanosis, unless the direction of the current is reversed by a pathological rise of pressure in the right heart or pulmonary artery producing a temporary or permanent reversal of flow, with a resultant transient or terminal cyanosis; III, Cyanotic Group (Morbus caeruleus) comprises all those cases in which the oxygen-unsaturation of the capillary blood is raised above its threshold value for the appearance of cyanosis (placed by Lungsgaard at 6.7 volumes per cent). Permanent cyanosis inevitably results from the direct admixture of venous blood with the arterial (venous-arterial shunt), comprising such lesions as septal defect with associated anomalies of right heart which raise the pressure above that on the left side, dextraposed or transposed aorta, biloculate and triloculate heart and persistent truncus arteriosus. Based upon this clinical classification Dr. Abbott gives a masterly description and analysis of cases falling into these three groups. Her book is the most complete exposition of the whole subject of congenital heart disease, and from it the practitioner will be enabled, as in no other way, to visualize the anatomical structure of cardiac disturbances of development and their pathological physiology and symptomatology. He will thus be enable to diagnose such lesions, and advise intelligent treatment and care. Further, his foundation for a broader cardiology will be immensely strengthened.

Cavernous Sinus Thrombophlebitis and Allied Septic and Traumatic Lesions of the Basal Venous Sinuses. A Clinical Study of Blood Stream Infection, By Wells P. Eagleton, M.D., Newark, N. J., Medical Director, Newark Eye and Ear Infirmary, Newark, N. J., Chief of the Division of Head Surgery, Newark City Hospital; Consulting Craniologist, St. Barnabas' Hospital, St. Michael's Hospital, Memorial Hospital, Beth Israel Hospital of Newark, N. Y.; Orange Memorial Hospital, Orange, N. J.; Muhlenberg Hospital, Plainfield, N. J.; and Mountainside Hospital, Mountclair, N. J. 196 pages, 17 figures and charts. The MacMillan Company, New York, 1926. Price in cloth, $3.00.

This monograph is the record of the author's personal experience in which he reviews his cases at length, placing special emphasis upon each and every diagnostic or operative error made. As he has learned chiefly through his failures he has laid especial stress upon these, so that others may profit from his experience. Inasmuch as thrombophlebitis of the cavernous sinus has up to the present time almost uniformly terminated fatally, he is persuaded that a study of the included cases will enable a diagnosis to be made early enough for rational surgery to be effectual, in a certain proportion of cases. His material consisted of 25 personally studied cases of cavernous sinus thrombophlebitis with 21 deaths and 4 recoveries. The chief object of this study is to emphasize the importance of the following considerations in the diagnosis and treatment of infective cavernous sinus disease. If the diagnosis is to be made early, which it must be if surgical intervention is to have the slightest chance of success, cavernous sinus phlebitis must be regarded as a group of diseases. For early diagnosis it must be appreciated that the classical symptoms of exophthalmos, edema of the lids and chemosis may or may not be present, depending on whether the sinus is sud-

denly and completely obstructed by an acute septic process, or gradually obliterated by a thrombus. An early diagnosis in the cases of slow involvement without classical symptoms of exophthalmos (the most promising type for surgical intervention) necessitates a careful study of the following mechanical factors which determine the symptomatology: (a), The path of entrance of the infection into the sinus; (b), the part of the sinus first attacked; (c), the alterations in the adjacent tissue that occur as the result of the venous anastomosis of the sinus. Finally, the necessity must be emphasized of placing the inflamed radicle at rest by ligation of the common or internal carotid artery, as well as treating the phlebitis by drainage. As to the frequency of cavernous sinus thrombophlebitis less than 300 cases had been recorded in the literature up to 1918; but it is very probable that it is not so infrequent if carefully sought for in septicemia and pyemia during life, or at autopsy following general blood stream infection. It must be realized that a septic clot may fill the cavernous sinus of both sides, the only symptom present being high, continuous temperature or chronic sepsis. The route of infection into the sinus may be opthalmic, pterygoid, sphenoidal, aural, tonsillar, and carotid venous plexus. Mixed types may occur. Each of these six types may or may not present the classical localizing symptoms of cavernous sinus thrombosis, in exophthalmos and chemosis, depending upon whether or not the circulation in the cavernous sinus is suddenly and completely occluded. Of particular importance to the general practitioner is the etiological relationship of operative trauma to cavernous sinus involvement and death, as in the case of staphylococcic furuncles and carbuncles of the face, particularly of the lip and nose. In these cases early operative incisions and squeezing in the early stages not only frequently fail to reveal pus in the furuncle, but have been followed by a rapid extension. Through dissemination of the bacteria the surgeon converts a local process into a general blood stream infection, which through a retrograde thrombophlebitis of the angular and facial veins, causes cavernous sinus involvement and death. Although this monograph deals with a highly specialized surgical procedure, the clinical aspects, as in the type just mentioned, are of the greatest importance to the practitioner, who usually is the one who sees the beginning of the infections leading to the involvement of the cavernous sinus, and, therefore, the basic knowledge herein contained should be familiar to him, so that he may make no diagnostic errors. The case histories contain much interesting and valuable material.

A Textbook of Biologic Assays. By Paul S. Pittenger, Ph.G., Ph.C., Ph.M., Phar.D., Instructor in Biologic Assaying, Philadelphia College of Pharmacy and Science, Philadelphia and Temple University Department of Pharmacy, Philadelphia; Member of the General Committee of Revision, Member of Subcommittee on Biological Assays, and Member of the Subcommittee on Biological Products and Diagnostical Tests of the Pharmacopoeia of the United States of America; Director of Pharmacological Research Laboratories of Sharp and Dohme; Chairman of the Physiological Testing Committee of the American Pharmaceutical Association; Member and Former Vice-President of the American Pharmaceutical Association; Chairman of the Committee on Pharmacology and Biologic Assays of the National Conference of Pharmaceutical Research. 373 pages, 153 illustrations, P. Blakiston's Son and Co., Philadelphia. Price in cloth, $3.00.

The first edition of this book was published in 1914; and at that time the subject of Biologic Assays was taught in very few Colleges of Pharmacy or Medicine, and was not recognized by the United States Pharmacopoeia or the National Formulary. At that time only a few experts engaged in the larger laboratories devoted to drug standardization were being employed in this work. The only official recognition previous to 1914 was taken by the United States Pharmacopoeial Convention of 1910 in recommending to the Revision Committee "that biologic tests or assays, when accuate and reliable may be admitted" to the U. S. P. IX. This recommendation resulted in the

inclusion of several optional and two compulsory Biologic Assays in that Pharmacopoeia. During the period in which the U. S. P. IX was official the various biologic assays methods were improved to a point where it was considered advisable, in the interest of uniformity, to make a greater number of methods compulsory. In the U. S. P. X compulsory biologic assays were included for the following drugs and preparations: Aconitine, Aconite and its tincture, Cannabis and its fluid extract, Digitalis and its tincture, Strophanthus and its tincture, Solution of Epinephrine Hydrochloride and Solution of Pituitary. Since under the provisions of the Pure Food and Drug Act, the standards of the Pharmacopoeia and the National Formulary are made Law for Interstate Commerce in drugs and medicines, the necessity for teaching the subject of Biologic Assays in all Schools of Pharmacy and Medicine is apparent. In the revision of this Manual, therefore, the wants of the pharmaceutical and medical colleges and their students have been the primary consideration. As in the first edition, methods familiar to experts but not referred to in the Pharmacopoeia or the literature with sufficient detail for students and beginners are fully described. It has been found necessary to rewrite practically the whole book, in order to include the many improvements in various methods, especially as to the technical details which have been developed since the first edition. This book should, therefore, adequately meet the present day requirements for a Textbook of Biologic Assays for students of Pharmacy and Medicine, and for those engaged in laboratories devoted to the biologic standardization of drugs.

College News Notes

The next ANNUAL MEETING of the AMERICAN COLLEGE OF PHYSICIANS will be held in Boston under the auspices of the Harvard Medical School during the week beginning April 8, 1929.

Drs. Aldred Scott Warthin, W. McKim Marriott, John H. Musser, Clement R. Jones, George Morris Piersol, Sydney R. Miller, William Gerry Morgan, F. M. Pottenger, John A. Lichty, Leonard M. Murray, Alfred Stengel, James H. Means, J. C. Meakins, James Alexander Miller, James S. McLester, John Phillips, Charles G. Jennings, President Martin, and the Executive Secretary, Mr. Loveland were present at the Regents' Meeting held in Washington, April 29, 1928.

NEW METHOD FOR PROPOSAL OF MEMBERS FROM THE ARMY, NAVY AND PUBLIC HEALTH SERVICES

At the New Orleans Session of the American College of Physicians, the Board of Regents adopted a resolution providing that candidates for membership from the Army, Navy and Public Health Services shall be proposed by the Surgeon General of each Service.

In establishing this method of proposal from these Services, it was thought that the Surgeon General will have at his disposal means of increasing morale and stimulating members of the Corps to better work. It is understood that there will be a limited number proposed each year from each Service, and that those selected will be men who have established a reputation for conspicuous ability and accomplishment or distinguished service as well as professional ability. Selection shall always be determined on the basis of professional merit and standing, character and reputation, and not necessarily on rank in the lineal list of medical officers. All candidates must meet the regular requirements prescribed by the Constitution and by the Committee on Credentials.

FELLOWS ELECTED AT THE NEW ORLEANS MEETING

Alvarez, Walter Clement, Rochester, Minn.
Arrasmith, W. W., Grand Island, Neb.
Balyeat, Ray M., Oklahoma City, Okla.
Bannick, Edwin G., Rochester, Minn.
Barborka, Clifford J., Rochester, Minn.
Bargen, J. A., Rochestre, Minn.
Barrow, John V., Los Angeles, Calif.
Bealer, Frank Rudisill, Washington, D. C.
Bell, Jess Vardeman, Kansas City, Mo.
Berkman, David M., Rochester, Minn.
Bitzer, E. W., Tampa, Fla
Bliss, Walter P., Pasadena, Calif.
Block, E. Bates, Atlanta, Ga.
Blumer, George, New Haven, Conn.
Bronfin, Isidor D. Denver, Colo.
Brown, Thomas R., Baltimore, Md.
Busby, J. L., Rochester, Minn.
Chambers, Wilfred E., Kansas City, Mo.
Campbell, J. Watson, Halstead, Kan.
Chapman, Lawrence Evans, Galveston, Texas
Christian, Henry A., Boston, Mass.
Cocke, Chas. Hartwell, Asheville, N. C.
Cole, James C. New Orleans, La.
Conner, Lewis A., New York, N. Y.
Corley, Cecil, Jackson, Miss.
Daley, Daniel Francis, Kingston, Pa.
Davis, Kenneth S., Los Angeles, Calif.
DeLorme, M. F., Brooklyn, N. Y.
Dibrell, John R., Little Rock, Ark.
Dickens, Paul Frederick, Washington, D. C.
Egan, William J., Milwaukee, Wis.
Emerson, Gouveneur V., Washington, D. C.
Falkowsky, Chas., Jr., Scranton, Pa.
Fenno, Frederick L., New Orleans, La.
Fontaine, Bryce W., Memphis, Tenn.
Foster, John H., Waterbury, Conn.
Freeman, Walter, Washington, D. C.
Geer, Everett K., St. Paul, Minn.
Giffin, Herbert Z., Rochester, Minn.
Gilliland, Charles E., St. Louis, Mo.

Gingold, David, Brooklyn, N. Y.
Glidden, Edson W., Alton, Ga.
Goldsmith, Milton, Pittsburgh, Pa.
Greene, Carl H., Rochester, Minn.
Greene, I. W., Owosso, Mich.
Guthrie, J. Birney, New Orleans, La.
Habein, H. C., Rochester, Minn.
Haft, Henry H., Syracuse, N. Y.
Hall, David C., Seattle, Wash.
Hangarter, Andrew H., Brooklyn, N. Y.
Harris, Titus Holliday, Galveston, Texas
Hartley, German Smith, Clifton Forge, Va.
Henderson, Walter F., New Orleans, La.
Hoff, A. E., North Bend, Neb.
Holbrook, Charles S., New Orleans, La.
Holmes, Paul McKinley, Toledo, Ohio
Horn, William Sullivan, Fort Worth, Texas
Houston, Wm. R., Augusta, Ga.
Hunter, James E., Seattle, Wash.
Joslin, Elliott R., Boston, Mass.
Kech, Augustus S., Altoona, Pa.
Kemper, C. F., Denver, Colo.
Kinney, Lyell C., San Diego, Calif.
Kirk, William Wilson, Jacksonville, Fla.
Lambright, Geo. L., Cleveland, Ohio
Levy, M. D., Houston, Texas
Libman, Emanuel, New York, N. Y.
Loewenberg, Samuel A., Philadelphia, Pa.
Longcope, Warfield T., Baltimore, Md.
Lorenz, Wm. F., Madison, Wis.
Lotz, Oscar, Milwaukee, Wis.
Luippold, Eugene J., Weehawken, N. J.
Lyon, George M., Huntington, W. Va.
Marbury, Charles C., Washington, D. C.
Marcovici, Eugene, New York, N. Y.
Marvin, H. Burns, Binghamton, N. Y.
Mason, E. H., Montreal, Canada
McCants, John M., Philadelphia, Pa.
McLean, C. C., Birmingham, Ala.
McLester, James S., Birmingham, Ala.
McNerney, Wm. J., Syracuse, N. Y.
Meakins, J. C., Montreal, Canada
Means, James H., Boston, Mass.
Meister, Wm. B., Fort Sam Houston, Texas
Melson, Oliver C., Little Rock, Ark.
Miller, Oscar O., Louisville, Ky.
Minot, George R., Boston, Mass.
Montrose, Frank J., Buffalo, N. Y.
Mundy, Carll S., Toledo, Ohio
Nesbit, William E., San Antonio, Texas
Nice, Charles M., Birmingham ,Ala.
Nichols, Estes, Portland, Maine
Norbury, Frank Garm, Jacksonville, Ill.
Norman, Estella G., Battle Creek, Mich.
O'Malley, Mary, Washington, D. C.
Palmer, Walter W., New York, N. Y.
Paullin, James Edgar, Atlanta, Ga.
Peabody, Jos. Winthrop, Washington, D. C.
Pearre, Albert Austin, Frederick, Md.
Perkins, Orman C., Brooklyn, N. Y.
Placak, J. C., Cleveland Heights, Ohio
Plummer, William A., Rochester, Minn.
Pomeranz, Maurice M., New York, N. Y.
Poust, Luther R., Fort Sam Houston, Texas
Quinn, James H., Springfield, Mass.
Rabinowitch, I. M., Montreal, Canada
Rainey, W. T., Fayetteville, N. C.
Ramsay, Robert E., Pasadena, Calif.
Reye, H. A., Detroit, Mich.
Roberts, George F., Salt Lake City, Utah
Root, J. Harold, Waterbury, Conn.
Rowntree, L. G., Rochester, Minn.
Ryan, John G., Denver, Colo.
Sanford, Arthur H., Rochester, Minn.
Sauls, H. C., Atlanta, Ga.
Sawyer, Carl W., Marion, Ohio
Schneider, Harvey C., Buffalo, N. Y.
Schonwald, Philipp, Seattle, Wash.
Schottstaedt, W. E. Richard, Fresno, Calif.
Schroeder, Frederick, Brooklyn, N. Y.
Sheppe, William Marco, Wheeling, W. Va.
Simon, Saling, Denver, Colo.
Simon, Sidney K. New Orleans, La.
Sledge, Edward S., Mobile, Ala.
Smith, H. Mason, Tampa, Fla.
Smith, Morgan, Little Rock, Ark.
Smythe, H. S., Bristol, Va.-Tenn.
Snader, Edward R., Jr., Philadelphia, Pa.
Sturgis, Cyrus C., Ann Arbor, Mich.
Taussig, Arnold S., Denver, Colo.
Taylor, Henry K., New York, N. Y.
Taylor, Raymond G., Los Angeles, Calif.
Taylor, John C., Chelsea, Okla.
Thayer, William S., Baltimore, Md.
Trossbach, Herman, Bogota, N. J.
Tucker, David Andrew, Jr., Cincinnati, Ohio
Ullman, Henry J., Santa Barbara, Calif.
Verity, Lloyd E., Battle Creek, Mich.
Vischer, Carl V., Philadelphia, Pa.
Walcott, Harry D., Dallas, Texas
Waring, James J., Denver, Colo.
Watts, H. C., Fort Harrison, Mont.
Webb, Gerald B., Colorado Springs, Colo.
Westcott, Leo Enos, Kalamazoo, Mich.
Whinery, Joseph B., Grand Rapids, Mich.
Williams, Lester James, Baton Rouge, La.

Williamson, G. Richard, New Orleans, La.
Whipple, George H., Rochester, N. Y.
Woltmann, Harro, Mansfield, Ohio
Wuerthele, Herman William, Pittsburgh, Pa.
Yampolsky, Joseph F., Atlanta, Ga.
Yegge, W. Bernard, Denver, Colo.
Zemp, E. R., Knoxville, Tenn.

ASSOCIATES ELECTED AT THE NEW ORLEANS MEETING

Ayers, Samuel, Los Angeles, Calif.
Babcock, Edward S., Sacramento, Calif.
Barthelme, Francis, Olney, Ill.
Bishop, Louis F., Jr., New York, N. Y.
Blaisdell, Elton R., Portland, Maine
Butler, H. Wesley, New Orleans, La.
Colomb, Henry O., National Soldiers Home, Va.
Coon, Harold M., Stevens Point, Wis.
Dunn, James N., St. Paul, Minn.
Emenhiser, J. L., Indiana Harbor, Ind.
Farnsworth, E. E., Grand Island, Neb.
Fife, Clinton D., Dayton, Ohio
Fisher, M. McC., Duluth, Minn.
Gamble, William G., Charleston, S. C.
Graves, Ghent, Houston, Texas
Hare, Herold P., Los Angeles, Calif.
Head, M. M., Zebulon, Ga.
Heninger, Ben R., Columbia, Miss.
Henry, Harvey R., Luling, Texas
Henske, Joseph A., Omaha, Neb.
Hill, Herbert, San Antonio, Texas
Horger, E. L., Columbia, S. C.
Howson, Carl R., Los Angeles, Calif.
Ireland, R. A., Charleston, W. Va.
Jaeger, Henry W., Washington, D. C.
Jeter, Hugh, Oklahoma City, Okla.
Krombein, Walter H., Buffalo, N. Y.
Leake, William H., Los Angeles, Calif.
Loomis, Edgar Webb, Dallas, Texas
Lounsberry, C. Ray, San Diego, Calif.
Maner, George, Los Angeles, Calif.
Matsger, Edward, San Francisco, Calif.
McIntire, Emery J., Carthage, Mo.
Miller, Tate, Dallas, Texas
Mogabgab, A., New Orleans, La.
Mowat, Kenneth G., Buffalo, N. Y.
Murphy, J. Harry, Omaha, Neb.
Otto, Frank W., Los Angeles, Calif.
Pigford, Russel C., New Orleans, La.
Pinney, George L., Hastings, Neb.
Reitzel, Raymond J., Galveston, Texas
Rohrbach, Harvey O., Bethelehem, Pa.
Rothschild, Karl, New Brunswick, N. J.
Sheppard, Thomas T., Pittsburgh, Pa.
Stites, Frank M., Louisville, Ky.
Susslin, Emil J., Bridgeport, Conn.
Waddell, James B., Indiana Harbor, Ind.
Wadsworth, John V., Buffalo, N. Y.
Ware, E. Richmond, Los Angeles, Calif.
Watson, Clyde E., Westwood, Calif.
Webster, John C., Los Angeles, Calif.
Wilson, R. E., Denver, Colo.
Winans, Leslie H., Ashland, Ky.

Dr. Hugh S. Cumming (Fellow 1923), Surgeon General of the United States Public Health Service, conducted a conference on April 9 at Washington for the discussion of methods and conditions of procedure in cancer research. A subcommittee consisting of Dr. Francis Carter Wood, New York; Dr. Warren H. Lewisof the Carnegie Institute; Dr. William H. Howell, Baltimore; Dr. James B. Murphy, New York, and Dr. Joseph W. Schereschewsky, Boston, was appointed to arrange a research program for early submission.

DELIVERED FIFTH HARVEY LECTURE

Dr. George R. Minot, F.A.C.P., Clinical Professor of Medicine of the Medical School of Harvard University delivered the fifth Harvey lecture before the New York Academy of Medicine, March 16. Dr. Minot's title was "The Treatment of Pernicious (Addison's) Anemia."

Dr. Minot was recently made Director of the Thorndike Memorial Laboratory at the Boston City Hospital, and has also been appointed Consulting Physician to the Peter Bent Brigham Hospital.

"Dr. Alfred Stengel, Philadelphia, was elected a member of the Board of Trustees of the University of Pennsylvani aon March 19, in recognition of his deep interest and great service to this institution in which he is head of the Department of Medicine. In but very few instances have members of the Faculty been elected to the Board of Trustees."

"Dr. Francis X. Dercum, Philadelphia, is President of the American Philosophical Society."

"Dr. Edward B. Krumbhaar, head of the Department of Pathology at the University of Pennsylvania, was recently elected Chairman of the Section in Medical History of the Philadelphia College of Physicians."

"Dr. C. J. Wiggers, head of the department of Physiology at Western Reserve University, Cleveland, Ohio, is reported to be conducting an interesting experiment with apparatus with which motion pictures of living heart beats can be made. An attempt is being made by which life can be restored to persons whose hearts have stopped beating due to electric shock."

Dr. Ross V. Patterson (Fellow), Dean of the Jefferson Medical College of Philadelphia, conducted a Heart Clinic at the April meeting of the Eighth District Medical Society of Greensboro, N. C.

Dr. James M. Anders (Master), of Philadelphia, has been appointed by the Secretary of Commerce, Hon. Herbert Hoover, as Chairman of a Committee to conduct a Better Homes Campaign.

Dr. Frederic W. Schlutz (Fellow), Professor of Pediatrics at the University of Minnesota Medical School, addressed the April meeting of the Milwaukee Pediatric Society on "Observations on Protein Metabolism in Nephroses."

Dr. Aldred Scott Warthin, First Vice-President of the College and Editor of the Annals presided at the meetings of the American Association for Cancer Research and the Association of American Physicians held in Washington in association with the Congress, April 30 and May 1, 2 and 3.

At a meeting of the Board of Regents of The College at Washington, D. C. on April 29, President Charles F. Martin appointed the following Fellows members of the Board of Governors to represent their respective states until the next regular election of Governors. Dr. Ernest E. Laubaugh, Boise, IDAHO; Dr. Thomas T. Holt, Wichita, KANSAS; and Dr. William M. James, Panama City (PANAMA and the CANAL ZONE).

The Board of Governors performs increasingly important functions in The College. It annually elects new members of the Board of Regents, the active governing body of The College, it recommends for election all incoming Associates, and it conducts other routine business which may be brought before it by the organization or the Board of Regents. Individual members of the Board of Governors investigate the records of all applicants from their respective states, and in various ways further the interests of The College in their localities.

Dr. B. W. Black (Fellow, 1927), resigned as Medical Director of the U. S. Veterans Bureau recently to accept an appointment as Medical Director of Alameda County, California. Dr. E. O. Crossman has succeeded Dr. Black as Medical Director of the Veterans Bureau.

Dr. Aristides Agramonte, Havana, Cuba, was among the many distinguished speakers and guests at the Twelfth Annual Clinical Session of The American College of Physicians at New Orleans. Dr. Agramonte is best known for his research in yellow fever and as a member of that distinguished group of army officers, including besides himself, Reed, Carroll, and Lazear, which was appointed by the United States to conduct its investigations in Cuba.

On March 12, during the Clinical Session, Tulane University honored Dr. Agramonte by conferring upon him the degree of Doctor of Laws, and the New Orleans Association of Commerce, at a luncheon, presented him with a life membership, engraved in gold, in recognition of the gratitude of New Orleans for his part in the investigation and control of yellow fever. Today yellow fever is practically unknown to occur in New Orleans, while preceding the appointment of the committee, and

their subsequent studies, a single epidemic of this disease caused more than four thousand deaths in New Orleans alone.

DR. ALDO CASTELLANI KNIGHTED

Announcement has recently been made that Dr. Aldo Castellani, F.A.C.P., Professor and Director of the Department of Tropical Medicine, Tulane University of Louisiana, School of Medicine, New Orleans, has had the honor of knighthood conferred upon him in recognition of his distinguished service to the British Government for work in the field of Tropical Medicine.

Though born n Florence, Italy, Dr. Castellani spent his youth in England, and later studied in Germany. He is credited as a discoverer of the "absorption test" for the differentiation of closely allied organisms. The British Government secured Dr. Castellani's services in conducting research on sleeping sickness in Africa, 1903. Later he was appointed Director of the Institute of Bacteriology at Colombo, Ceylon, and still later became head of the clinic of tropical diseases and conducted numerous researches.

Dr. Castellani is joint author with Dr. Albert J. Chalmers of "Manual of Tropical Medicine," a widely known publication.

From 1914 to 1919, he was Professor of Tropical Medicine at the Royal University at Naples, and thereafter lecturer on Mycoses, at the London School of Tropical Medicine. During the World War, he served as Lieutenant Colonel in the medical service of the Italian Navy. In 1925, he was appointed to the chair of Professor of Tropical Medicine at Tulane.

OBITUARY

Dr. Adam Joseph Simpson, Chester, Pennsylvania, (Fellow, April 1, 1923). Died April 6, of Heart Disease; age 49.

Dr. Simpson received his medical degree from the Gross Medical College, Denver, in 1901 and later pursued postgraduate study at the Graduate School of Medicine of the University of Pennsylvania and at the Massachusetts General Hospital. From 1904 to 1914, he was a member of the Medical Dispensary Staff of the University of Colorado School of Medicine. Later he removed to Chester, Pennsylvania, where he was a member of the Medical Staff of the Chester Hospital, from 1916 until the time of his death. He was a member of his County and State Medical Societies, and a Fellow of The American Medical Association.

With the appearance of the June number of ANNALS OF INTERNAL MEDICINE, Volume I will be completed. It is important that notice of renewal of subscription for a continuance of Volume II be sent promptly to the Executive Secretary, Mr. E. R. Loveland, 37th & Chestnut Streets, Philadelphia, Pa.

The Journal is occupying a high place among publications on Internal Medicine, as evidenced by its increased demand and rapidly growing circulation.

ADVERTISING IN ANNALS

The Board of Regents and the Publication Committee of The College have expressed the wish to have advertising in Annals of Internal Medicine promoted among publishers of high grade medical books and manufacturers of the most reputable instruments and therapeutic products. Publishers and manufacturers have not hitherto realized the possibilities of advertising through this medium, nor have they taken into consideration the preferred class our subscribers and members represent.

The College does not seek the advertisements of any but the highest type. To this end, the following committee on advertising censorship has been appointed:

Harlow Brook, New York
Edward J. G. Beardsley, Philadelphia
George Morris Piersol, Philadelphia

All inquiries and communications concerning advertising should be sent to the Executive Secretary, Mr. E. R. Loveland, who will be aided by the above committee. Advertising rates and contract forms will be sent upon request. Members of The College are urged to co-operate in securing the advertising which will prove helpful to the journal, and aid somewhat in defraying the costs of publication.

NO NEW EDITION OF YEAR BOOK FOR 1928

The Board of Regents, at a meeting in April at Washington, D. C., determined to print the YEAR BOOK of The American College of Physicians only every two years. Inasmuch as the last edition was printed during the summer of 1927 and dated "1927-28," there will not be another edition before the summer of 1929 for "1929-30." However, the Executive Secretary will prepare a suitable supplement containing all elections, changes in membership, biographical data, etc., and distribute it early in September. This supplement will be prepared in suitable form for inserting in the 1927-28 YEAR BOOK, thus giving all members a complete directory.